Nelson's Neonatal Antimicrobial Therapy

2nd Edition

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Jason Sauberan, PharmD
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Published by the American Academy of Pediatrics
345 Park Blvd
Itasca, IL 60143
Telephone: 630/626-6000
Facsimile: 847/434-8000
www.aap.org

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First edition published 2019; second edition, 2024.
Printed in the United States of America

9-506/0324 1 2 3 4 5 6 7 8 9 10
MA1121
ISBN: 978-1-61002-698-7
eBook: 978-1-61002-699-4

Library of Congress Control Number: 2023950173

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Introduction

Although many data gaps challenge our ability to make an optimal choice of therapy and dosage for every neonate with suspected or proven infection, we realize that in clinical care a treatment decision must be made. With that in mind, our goal for *Nelson's Neonatal Antimicrobial Therapy* is to provide answers that help those taking care of neonates make the best possible treatment decisions. Our recommendations are based on the best available evidence and the breadth of clinical experience among the editorial team. How strongly we feel about a recommendation and the strength of the evidence to support a recommendation are graded throughout the book according to the following Table:

Strength of Recommendation	Description
A	Strongly recommended
B	Recommended as a good choice
C	One option for therapy that is adequate, perhaps among many other adequate therapies
Level of Evidence	**Description**
I	Based on well-designed, prospective, randomized, and controlled studies in an appropriate population of children
II	Based on data derived from prospectively collected, small comparative trials, or noncomparative prospective trials, or reasonable retrospective data from clinical trials in children, or data from other populations (eg, adults)
III	Based on case reports, case series, consensus statements, or expert opinion for situations in which sound data do not exist

The genesis of a second edition of *Nelson's Neonatal Antimicrobial Therapy* is a testament to the fact that neonatal infectious disease therapeutics research is continuously expanding. Since the first edition was released just a few years ago, bacterial resistance has increased, new therapeutic options have reached the front lines, and novel pathogens have emerged—including the novel coronavirus pandemic that began in 2019. Readers looking for additional sources of new information are encouraged to visit the following websites (all accessed October 26, 2023):

- Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org)
- Global Antibiotic Research & Development Partnership (https://gardp.org/childrens-antibiotics)
- Institute for Advanced Clinical Trials for Children (https://iactc.org)
- International Neonatal Consortium (https://c-path.org/programs/inc)
- Organization of Teratology Information Specialists MotherToBaby (https://mothertobaby.org)

- Pediatric Trials Network (https://pediatrictrials.org)
- Pew Charitable Trusts Antibiotic Resistance Project (www.pewtrusts.org/en/projects/antibiotic-resistance-project)
- Trial registers (https://clinicaltrials.gov; https://health-products.canada.ca/ctdb-bdec; www.clinicaltrialsregister.eu)
- US Food & Drug Administration Medical Products for Newborns (www.fda.gov/science-research/pediatrics/medical-products-newborns)

We are interested to learn from readers about the readability and clinical usefulness of this book. Please send suggestions and comments to nelsonabx@aap.org.

We would like to thank the American Academy of Pediatrics (AAP) publishing staff, especially Senior Editor, Professional and Clinical Publishing, Mary Kelly, for their leadership and support throughout the development and launch of this second edition of *Nelson's Neonatal Antimicrobial Therapy*. Thanks to Mark Grimes, vice president, Publishing, and our steadfast friends and supporters in AAP Membership, Marketing, and Publishing—Jeff Mahony, senior director, professional and consumer publishing; Mary Louise Carr, marketing manager, clinical publications; and the entire staff—for their support of this new publication.

Finally, we owe a tremendous debt to John S. Bradley, MD, the editor in chief, and John D. Nelson, MD, the founder of *Nelson's Pediatric Antimicrobial Therapy*. Without their dedication to optimizing antibiotic use in children this book—much less a second edition—would never have become a reality. In addition, we appreciate the extensive time and expertise our contributing editors provided. It is our hope that *Nelson's Neonatal Antimicrobial Therapy* will live up to the legacy of its literary parent, *Nelson's Pediatric Antimicrobial Therapy*. Our aim is to be consistent with the "Antimicrobial Therapy for Neonates" chapter in *Nelson's Pediatric Antimicrobial Therapy* while providing a wider and deeper range of neonatal content. We hope that *Nelson's Neonatal Antimicrobial Therapy* will serve as a valuable resource for all providers who care for newborns.

Joseph B. Cantey, MD, MPH

Jason Sauberan, PharmD

Abbreviations

3TC, lamivudine

ABLC, amphotericin B lipid complex (Abelcet)

AKI, acute kidney injury

ALT, alanine aminotransferase

AmB, amphotericin B

AmB-D, amphotericin B deoxycholate

amox/clav, amoxicillin/clavulanate (Augmentin)

AST, aspartate transaminase

AUC, area under the curve (the mathematically calculated area under the serum concentration-versus-time curve)

AUC_{12}, AUC during a 12-hour dosing period

AUC_{24}, AUC during a 24-hour dosing period

bid, twice daily

BIG-IV, botulism immune globulin intravenous

BPD, bronchopulmonary dysplasia

BSA, body surface area

CBC, complete blood cell count

CDC, Centers for Disease Control and Prevention

CLABSI, central line–associated bloodstream infection

CMV, cytomegalovirus

CNS, central nervous system

conc, concentration

CSF, cerebrospinal fluid

CYP, cytochrome P450

D5W, dextrose 5% in water

div, divided

DOL, day of life

DOT, directly observed therapy

ECMO, extracorporeal membrane oxygenation

EONS, early onset neonatal sepsis

ESBL, extended-spectrum beta-lactamase

FDA, US Food and Drug Administration

FQ, fluoroquinolone

G6PD, glucose-6-phosphate dehydrogenase

GA, gestational age

GBS, group B streptococcus

G-CSF, granulocyte colony-stimulating factor

GFR, glomerular filtration rate

HBsAg, hepatitis B surface antigen

HBV, hepatitis B virus

HIE, hypoxic-ischemic encephalopathy

HIV, human immunodeficiency virus

HSV, herpes simplex virus

IAI, intra-abdominal infection

IC_{50}, half maximal inhibitory concentration

ID, infectious disease

IM, intramuscular(ly)

IQR, interquartile range

IUGR, intrauterine growth restriction

IV, intravenous(ly)

IVIG, intravenous immune globulin

L-AmB, liposomal amphotericin B

LPV/r, lopinavir/ritonavir

LRTI, lower respiratory tract infection

MIC, minimum inhibitory concentration

MRSA, methicillin-resistant *Staphylococcus aureus*

MSSA, methicillin-susceptible *Staphylococcus aureus*

NEC, necrotizing enterocolitis

NICU, neonatal intensive care unit

NVP, nevirapine

PAE, post-antimicrobial effect

PCR, polymerase chain reaction

PD, pharmacodynamic(s)

PDA, patent ductus arteriosus

pip/tazo, piperacillin/tazobactam

PK, pharmacokinetic(s)

PMA, postmenstrual age (weeks of gestation since most recent menstrual period PLUS weeks of chronologic age since birth)

PNA, postnatal age

PNAC, parenteral nutrition associated cholestasis

PO, oral(ly)

q, every

qd, once daily

qid, 4 times daily

QTc, corrected QT interval

RAL, raltegravir

RPR, rapid plasma reagin

RSV, respiratory syncytial virus

SCr, serum creatinine

spp, species

tab, tablet

TB, tuberculosis

TH, therapeutic hypothermia

tid, 3 times daily

TIG, tetanus immune globulin

TMP/SMX, trimethoprim/sulfamethoxazole

UCSF, University of California, San Francisco

ULN, upper limit of normal

UOP, urine output

UTI, urinary tract infection

VDRL, Venereal Disease Research Laboratories

VZV, varicella-zoster virus

WHO, World Health Organization

ZDV, zidovudine

1. Choosing an Antibiotic for the Neonate

Optimizing antibiotic use in neonates is a complex task. To select the ideal treatment for suspected or proven infection, health care professionals must weigh a variety of factors. These include the rapidly changing physiology, volume of distribution, and antibiotic clearance of newborns; the susceptibilities of the offending pathogen(s); whether or not a given antibiotic penetrates the infected body compartment (eg, into cerebrospinal fluid); the toxicity of the antibiotic regimen; and the short- and long-term effects of antibiotic exposure on the neonate's microbiome. *Nelson's Neonatal Antimicrobial Therapy* aims to help health care professionals select the right drug, dose, and duration for neonates.

This chapter provides an overview of antibiotic selection and a primer on the types and classes of antibacterials and antifungals commonly used in neonates.

New drugs should be compared with others in the same class regarding antimicrobial spectrum, efficacy, toxicity, and cost. If there is no substantial benefit to efficacy or safety for one antimicrobial over another, health care professionals are encouraged to opt for an older, more extensively used, and less expensive drug with the narrowest spectrum of activity.

Antibacterials

Beta-lactams

Penicillin. Penicillin is still highly active against group B or group A *Streptococcus* and syphilis (*Treponema pallidum*). Many strains of *Streptococcus pneumoniae* are susceptible to penicillin, although this should not be assumed.

Aminopenicillins. Amoxicillin (± clavulanate) and ampicillin (± sulbactam) have activity against streptococcal species and *Enterococcus.* The addition of beta-lactamase inhibitors (clavulanate or sulbactam) provides coverage against some gram-negative beta-lactamase–producing organisms such as *Haemophilus influenzae,* selected anaerobes (including *Bacteroides fragilis*), and methicillin-susceptible *Staphylococcus aureus* (MSSA). However, ampicillin/sulbactam has limited activity against enteric bacilli and has not been well studied in neonates.

Penicillinase-Resistant Penicillins. Also known as "semisynthetic penicillins"; oxacillin and nafcillin have activity against the beta-lactamase produced by MSSA. They also cover streptococci. They are not effective against methicillin-resistant *S aureus* (MRSA), coagulase-negative staphylococci (CoNS), or *Enterococcus;* nor do they have activity against gram-negative organisms.

Antipseudomonal Penicillins. Piperacillin/tazobactam is a penicillin-class agent with activity against *Pseudomonas* and many other oxidase-positive gram-negative bacilli, *Enterococcus,* and, due to the beta-lactamase inhibitor tazobactam, anaerobes and many extended beta-lactamase–producing enteric bacilli. It also has some activity against MSSA.

First-generation Cephalosporins. Cephalexin and cefazolin have activity against MSSA and most streptococci. They do not have activity against MRSA, CoNS, or *Enterococcus.* Their gram-negative coverage is limited but better than ampicillin. Cefazolin may have reduced activity in infections with a high bacterial inoculum due to overproduction of a beta-lactamase that inactivates cefazolin to a greater degree than oxacillin or nafcillin. Cefazolin also has limited central nervous system penetration and is unlikely to be effective in the treatment of meningitis caused by MSSA or susceptible gram-negative bacteria.

Second-generation Cephalosporins. Cefuroxime and the cephamycins, cefoxitin and cefotetan, retain the coverage of first-generation agents but also have increased activity against gram-negative organisms, including *Escherichia coli* and *Haemophilus.* Cefuroxime is inferior to third-generation cephalosporins for treatment of meningitis. The cephamycins have reasonable anaerobic coverage, including most strains of *Bacteroides fragilis.* However, other anti-anaerobic agents such as metronidazole, piperacillin/tazobactam, and carbapenems are more active against anaerobes and are better studied in neonates.

Third-generation Cephalosporins. Cefotaxime, ceftriaxone, and ceftazidime all have enhanced activity against enteric gram-negative bacilli, such as *E coli, Klebsiella,* and non–extended-spectrum beta-lactamase (ESBL)–producing *Enterobacter* or *Citrobacter.* They all cross the blood-brain barrier and can be used to treat gram-negative meningitis. Ceftazidime is the only third-generation cephalosporin with activity against *Pseudomonas,* but it is less active against group B *Streptococcus* than cefotaxime. Ceftazidime combined with the beta-lactamase inhibitor avibactam has activity against ceftazidime-resistant, ESBL-producing, and OXA-48 carbapenemase–producing gram-negative bacteria. Avibactam has not been well studied in neonates.

Fourth-generation Cephalosporins. Cefepime has all the coverage of cefotaxime and ceftriaxone with the addition of antipseudomonal activity. Cefepime crosses the blood-brain barrier and can be used to treat gram-negative meningitis. Although it has slightly broader spectrum (due to its activity against *Pseudomonas*), cefepime may be used in place of cefotaxime if cefotaxime is unavailable.

Fifth-generation Cephalosporins. Ceftaroline has activity against a variety of gram-positive infections, including MRSA. Its activity against gram-negative infections is somewhat less than the third- and fourth-generation cephalosporins.

Ceftolozane/tazobactam is an antipseudomonal agent with activity against AmpC beta-lactamase–expressing, ceftazidime-resistant isolates and efflux pump–expressing, carbapenem-resistant isolates but not OXA-48 carbapenemases.

Like all cephalosporins, ceftaroline and ceftolozane do not have activity against *Enterococcus.*

Aztreonam. Aztreonam is the only available monobactam agent. It has activity against aerobic gram-negative bacilli, including *E coli* and *Pseudomonas aeruginosa*, but it is

not active against gram-positive bacteria, anaerobes, or ESBL-producing gram-negative bacilli. Aztreonam has good central nervous system penetration and is effective in treating gram-negative meningitis.

Carbapenems. Meropenem and imipenem are broadly active agents that have activity against gram-negative bacilli (including *Pseudomonas* and ESBL-producing gram-negative bacilli), most gram-positive infections other than MRSA or *Enterococcus,* and anaerobes including *Bacteroides.* In general, carbapenems should be reserved for ESBL-producing gram-negative bacilli because narrower-spectrum agents are effective for other bacteria. See Chapter 2 for additional potential uses. Carbapenem-resistant gram-negative bacilli have already emerged and spread to many parts of the world, highlighting the need to keep track of your local antibiotic susceptibility patterns.

Aminoglycosides

Three aminoglycosides are widely used for systemic treatment of gram-negative infections or for synergy in the treatment of certain gram-positive infections: gentamicin, amikacin, and tobramycin. A fourth, streptomycin, is used for tuberculosis.

Gentamicin is the single most-used antibiotic in the nursery setting because it has a role in the empiric treatment of both early- and late-onset sepsis as well as many focal infections. Aminoglycosides do not achieve sufficiently high concentrations in spinal fluid and, therefore, are not used for monotherapy of meningitis, although gentamicin is used for synergy against group B streptococcal meningitis. Aminoglycosides do not have activity against obligate anaerobes (eg, *Bacteroides*). Therapeutic drug monitoring is necessary to ensure that the concentration is sufficient to achieve bacterial killing (see Chapter 2).

Macrolides

Erythromycin and azithromycin are used in the treatment of *Bordetella pertussis* and *Chlamydia trachomatis* in neonates. Azithromycin also has some activity against certain gram-negative bacilli, including enteric pathogens such as *Salmonella* and *Shigella.* Azithromycin is increasingly used in combination therapy against *Neisseria gonorrhoeae* due to rising cephalosporin resistance. These drugs achieve high intracellular concentrations and have relatively long half-lives, particularly azithromycin. Exposure to erythromycin and, to a lesser degree, azithromycin in the first 6 weeks after birth has been associated with the development of pyloric stenosis.

Glycopeptides

Vancomycin has activity only against gram-positive organisms, including MRSA and *Enterococcus.* It has activity against MSSA, although it is inferior to the penicillinase-resistant penicillins (eg, oxacillin) for this purpose. Therapeutic drug monitoring is necessary to ensure that the concentration is sufficient to achieve bacterial killing (see Chapter 2). Vancomycin crosses the blood-brain barrier; when used for meningitis, higher serum concentrations are necessary to achieve adequate concentrations in the cerebrospinal fluid.

Common Bacterial Pathogens and Their General Susceptibility to Common Antibacterial Agents Used in Neonates[a]				
	Penicillins			
	Penicillin	Aminopenicillin	Penicillinase-resistant	Antipseudomonal
Gram-positive				
MSSA		Partial[b]	Yes	Partial
MRSA				
Streptococcus spp	Yes	Yes	Yes	Yes
Enterococcus		Yes		Yes
Anaerobes	Partial	Partial	Yes	Yes
Gram-negative				
Escherichia coli and other enteric gram-negative bacilli		Partial		Yes
Pseudomonas				Yes
Anaerobes (including *Bacteroides*)				Yes

	Cephalosporins							
	First-generation	Second-generation	Third-generation	Fourth-generation	Fifth-generation	Carbapenems	Amino-glycosides	Glycopeptides
Gram-positive								
MSSA	Yes	Yes			Yes	Yes		Yes[c]
MRSA					Yes			Yes
Streptococcus spp	Yes	Yes	Yes	Yes	Yes	Yes	Synergy	Yes
Enterococcus								Yes
Anaerobes	Yes	Yes	Yes	Yes	Yes	Yes		Yes
Gram-negative								
Escherichia coli and other enteric gram-negative bacilli	Partial	Partial	Yes	Yes	Partial	Yes	Yes	
Pseudomonas				Yes		Yes	Partial[d]	
Anaerobes (including *Bacteroides*)			Partial	Partial		Yes		

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus;* spp, species.

[a] Blank cells imply generally not susceptible. Not all agents listed; see chapter text for more details.

[b] Aminopenicillins with beta-lactamase inhibitors (eg, clavulanate, sulbactam) have limited activity against MSSA.

[c] Penicillinase-resistant penicillins (eg, oxacillin, nafcillin) and first-generation cephalosporins (eg, cefazolin) are superior to vancomycin for the treatment of MSSA.

[d] Tobramycin has activity against most strains of *Pseudomonas*.

Dalbavancin is a long-acting lipoglycopeptide with similar activity to vancomycin. It is administered as a one-time dose and could be considered for use in term neonates with skin infections due to susceptible gram-positive organisms, particularly if ongoing intravenous access is not possible.

Other Agents

Linezolid and rifampin are antistaphylococcal, anti-enterococcal agents with niche uses in treatment of drug-resistant isolates, including MRSA and vancomycin-resistant *Enterococcus,* and in nondrug-resistant but difficult-to-treat infections due to biofilms. They are uncommonly used in neonates, although they are both US Food and Drug Administration approved and have neonatal dosing recommendations. Rifampin is typically used in combination with other agents due to resistance that can develop during monotherapy.

Antifungals

Amphotericin B

Amphotericin B (AmB) is the most broad-spectrum antifungal agent available for clinical use. Amphotericin B has broad activity against *Candida* (except for *C lusitaniae*), *Aspergillus* (except for *A terreus*), and *Zygomycetes* (eg, *Mucor, Rhizopus*). One of the primary advantages of AmB over other agents is that it has been used for decades in neonates, in contrast to newer agents like the echinocandins.

Toxicity of AmB in humans comes from cross-reactivity with sterols in human cells, which leads to disruption of lipid bilayers on the outer membrane and within the cell. The conventional formulation, AmB deoxycholate (AmB-D), causes significant toxicity in older children but is generally well tolerated in neonates. Lipid-based AmB formulations are used in older children to mitigate side effects, but limited retrospective data suggest that AmB-D is more efficacious in neonates. AmB-D also has better renal penetration than the lipid forms, which is relevant when treating neonatal fungal infections that involve the kidneys or bladder.

Azoles

Fluconazole. Fluconazole has activity against many strains of *Candida* (including *C albicans, C parapsilosis, C tropicalis,* and some strains of *C glabrata*). It achieves relatively high concentrations in both urine and cerebrospinal fluid. All *C krusei,* most *C auris,* and some *C glabrata* strains are resistant to fluconazole. In addition, fluconazole should not be used for treatment of breakthrough infections among neonates receiving fluconazole prophylaxis because those yeasts may have developed fluconazole resistance.

Voriconazole. Voriconazole is fungicidal against yeast and molds but is primarily used in neonates as first-line treatment of the mold *Aspergillus*. Voriconazole has excellent tissue, urine, and cerebrospinal fluid penetration. However, the enteric absorption and hepatic clearance of voriconazole varies substantially among patients. Therapeutic trough monitoring is necessary. Most experts suggest that trough concentrations of 2 to 6 mcg/mL

are ideal; activity decreases at concentrations below 1 mcg/mL, and toxicity is more common at concentrations above 6 mcg/mL. The pharmacokinetics of voriconazole have not been well studied in neonates.

Echinocandins

The echinocandins micafungin, caspofungin, and anidulafungin have activity against most yeasts such as *Candida* (although resistance rates in certain *Candida* species are rising) and have been used in salvage therapy against molds such as *Aspergillus*. Echinocandins inhibit fungal cell wall formation by inhibiting beta-1,3-glucan synthase, an enzyme that is not present in human cells. As a result, these agents are generally well tolerated. However, the echinocandins do not have reliable penetration into the cerebrospinal fluid or urine; thus, their use in the neonatal intensive care unit is limited. Among the echinocandins, micafungin is the best studied in neonates. Anidulafungin is not currently recommended for neonates due to uncertainty of the optimal dosage and the potential for toxicity from the polysorbate-80 solvent used in the commercially available product.

2. Antimicrobial Drug Therapy for Neonates

NOTES

- This chapter focuses on neonatal antimicrobial clinical pharmacology, dosages, administration, and formulations. The reader is encouraged to cross-reference the relevant portions of other chapters to be familiar with the appropriate use of a given drug for a given condition, including management of key adverse drug reactions.

A. NEONATAL PHARMACOKINETICS

Pharmacokinetics (PK) refers to a drug's dose-exposure relationships—the changes in drug concentration that occur over time after a drug is administered. Neonatal PK characteristics are influenced by gestational and postnatal developmental changes in body composition and organ function. Developmental stage variability between patients in the NICU creates a challenge where each neonate may require a unique dose or frequency of an antimicrobial agent to achieve the target antibiotic exposure associated with clinical and microbiologic success.

The following Table summarizes how antimicrobial PK parameters are affected by a neonate's unique developmental traits, their clinical relevance, and dosing approaches that stem from these. Non-developmental disease and iatrogenic effects in neonates are also included.

PK Parameter	Neonatal Trait	Clinical Relevance	Prescribing Strategy	Disease and Iatrogenic Effects
Absorption	**PO:** hypochlorhydria, delayed gastric emptying, decreased motility, reduced bile acid. **IM:** reduced muscle contractility, higher muscle water content, increased muscle capillary density. **Skin:** Thinner stratum corneum, increased skin perfusion, higher BSA to weight ratio. All inversely related to GA.	**PO:** slower absorption, increased absorption of acid labile drugs, futility of dosing on "empty stomach" **IM:** slower absorption and lower peak conc, greater total absorption of water-soluble antibiotics **Skin:** undesirable systemic absorption including excipients	**PO:** Route usually avoided except for a few low-risk indications (see Chapter 3). **IM:** acceptable but not ideal if need rapid, high conc (eg, meningitis). **Skin:** care when using certain antiseptics (eg, chlorhexidine), choosing topical antibiotics that have clinical safety evidence in neonates (eg, bacitracin, nystatin).	**IM:** Septic shock decreases muscle perfusion and reduces IM absorption.
Distribution	Increased body water and extracellular fluid; reduced fat and muscle mass (inversely related to GA) Reduced protein binding Higher cerebral blood flow, lower brain vessel P-glycoprotein efflux transporter activity	Larger drug distribution volumes Efficacy and toxicity achievable with lower total plasma conc compared with adults due to less protein binding and greater free fraction (eg, **cefazolin**, **vancomycin**)[a] Possibly greater CNS penetration	Loading doses and higher maintenance doses per kg for water-soluble drugs to achieve target exposures (eg, aminoglycosides, vancomycin)	ECMO, PDA increase volumes of drug distribution, reducing drug conc. Hyperbilirubinemia can displace protein-bound drug, and vice versa.[b]

Clearance	Reduced GFR (GFR related to GA), renal tubule active transport, CYP, glucuronidation, and P-glycoprotein activity. Birth triggers rapid increase in GFR (slower in preterm neonates due to incomplete nephrogenesis) and some CYP isoforms. Sulfation fully active. Reduced protein binding.	Slower clearance, longer half-life Paradoxical increased clearance in some drugs due to lower protein binding[c] Reduced nephrotoxicity from decreased tubular reabsorption (eg, aminoglycosides)	Longer intervals initially that shorten as PNA increases. Interval shortening happens at earlier PNA in term neonates compared with preterm neonates. Larger daily doses needed for some drugs to overcome increased clearance due to reduced protein binding (eg, **micafungin**).[c]	Asphyxia, hypotension, PDA; reduce GFR and renal drug clearance. TH may reduce clearance.[d] Indomethacin, ibuprofen decrease clearance of renally eliminated drugs. Formula feeding increases CYP expression compared with human milk.

[a] Targeting concentrations for these drugs in PK studies based on adult total (bound and free) concentration targets underestimates the unbound (free) exposure in the neonate.

[b] Although most drugs have reduced plasma protein binding in neonates compared with children and adults, some are still relatively highly protein bound and can compete with bilirubin for albumin-binding sites. Displacing bilirubin from albumin binding increases free, unbound bilirubin, which can increase the risk of kernicterus, particularly in the septic, acidotic neonate. Sulfisoxazole was first recognized in 1956 as causing kernicterus as a result of bilirubin displacement. Another sulfonamide antimicrobial, **TMP/SMX,** is labeled as contraindicated in neonates in the United States and Canada due to its potential for bilirubin displacement and concerns over kernicterus, as well as noninclusion of neonates and infants <2 mo in prospective clinical pediatric trials. However, in vitro studies indicate that concentrations of SMX needed for displacement are well above therapeutic concentrations in neonates. TMP/SMX has been widely used globally for neonatal sepsis and pneumonia, and there are no reports of kernicterus from its clinical use. For neonates who are not clinically ill, with resolving neonatal jaundice and low-risk serum bilirubin concentrations, the use of TMP/SMX is reasonable in situations for which other PO or IV therapy is not available or other options are potentially more toxic. **Ceftriaxone** is similarly labeled as contraindicated because of its known high protein binding and bilirubin displacement potential, but it is also used globally for neonatal sepsis and there are no cases of kernicterus reported. Other antimicrobials with strong displacement potential but which do not carry a labeled warning include cefazolin and oxacillin.

[c] Unlike renally eliminated antibiotics such as vancomycin and cefazolin that have developmentally immature renal clearance compared with adults, micafungin hepatobiliary clearance maturity and capability are the same as adults. The developmentally reduced protein binding of micafungin creates a situation in which more unbound (free) drug is available to undergo hepatobiliary excretion and, hence, its clearance is higher per kg compared with adults.

[d] PK studies of renally eliminated antibiotics in neonates being treated with TH for HIE suggest that Cl is altered during TH. This is consistent with animal model studies, which demonstrate that GFR is reduced when hypothermia is applied. However, since HIE can cause reversible AKI, it is not clear from the neonatal TH PK studies to what extent TH independently contributes to altered clearance, or if TH is a proxy for underlying illness severity. There have been no comparisons with non-HIE neonates who do not receive TH matched for illness severity to know for sure. Considering that EONS contributes to the risk of brain injury in neonates with HIE, we do not recommend TH-triggered conservative empiric antibiotic dosing until better data are available. Clinicians should apply standard therapeutic drug monitoring practices (see Therapeutic Drug Monitoring) to any neonate with confirmed or suspected AKI.

Pharmacogenetics. Variation in drug metabolizing, transport, or binding protein phenotypes can contribute to altered PK and clinical response. Genetic testing to identify individuals with clinically relevant phenotypes allows for selection of drug regimens that are safer or more effective compared with standard regimens. Pharmacogenetic testing currently has the potential for individualized dosing of numerous *nonantibiotics* in neonates and infants (eg, tramadol, morphine, proton pump inhibitors) but has not yet been integrated into neonatal antimicrobial prescribing as it has in older children (eg, voriconazole, atazanavir, primaquine). In locations where newborn screening for G6PD deficiency is routinely performed, the potential for pharmacogenetic-guided neonatal therapy exists since nitrofurantoin is to be avoided (including via human milk) in patients with this common enzymopathy. Screening for *MT-RNR1* genetic variants associated with an increased risk of aminoglycoside-induced hearing loss represents a future potential use of antenatal pharmacogenetic testing.

B. ANTIMICROBIAL PHARMACODYNAMICS

Pharmacodynamics (PD) refers to a drug's exposure-effect relationship. Knowledge of antimicrobial PD characteristics allows for good decision-making when selecting a dosage regimen. In neonates, PD principles are applied in the clinical setting when accounting for PK differences related to gestational and postnatal age. For example, the extremely preterm baby's larger distribution volume may require a higher **gentamicin** dose per kg to achieve the target peak concentration compared with a term baby, and a 5-week-old's higher clearance will require more frequent **cefepime** dosing to maintain concentrations above the MIC compared with a newborn.

The following Table summarizes the established PD doctrine for antimicrobial agents. However, there are some caveats to consider when applying PD concepts in neonates.

- Factors other than PD determine a drug's efficacy. These factors include organism population size, rate of organism adaptive resistance and regrowth, bactericidal effects, and host immune defenses.
- Pharmacodynamic characteristics are typically determined using in vitro or animal infection time-kill studies that don't apply neonatal PK parameters when experimentally creating concentration versus time conditions. The recommended optimal PD targets are, thus, not entirely generalizable to neonates.

	PD Characteristic		
	Time Dependent	**Conc Dependent**	**AUC Dependent[a]**
Meaning	Activity related to amount of time drug conc is >MIC	Activity related to peak conc of drug relative to MIC	Activity related to AUC_{24} relative to MIC
PAE	Short or none	Long	Long
Dosing strategy	Frequent dosing to maintain conc >MIC for an adequate % of the dosing interval[b]	High enough dose to achieve target ratio of peak conc to MIC[c]	Designed to achieve target ratio of AUC_{24} to MIC[d]
Examples[e]			
Antibacterial	β-lactams,[f] erythromycin, vancomycin[g]	Aminoglycosides,[h] FQs,[i] metronidazole	Azithromycin, clindamycin, linezolid, vancomycin[g]
Antifungal	Flucytosine	Amphotericin B	Azoles[j]

[a] Drugs that are not concentration dependent and have a long PAE, which minimizes the importance of their time dependence.

[b] Usually set at 70%–75% for neonates, based on decreased neonatal humoral, cellular, and neutrophil function. For an immunocompetent pediatric or adult host, the %T>MIC is generally 40% for most beta-lactam antibiotic-pathogen pairs.

[c] PAE allows for less frequent dosing.

[d] Target experimentally determined and unique for each drug.

[e] Focusing on drugs used in neonates, not an all-inclusive list.

[f] For example, ampicillin, penicillin, cephalosporins, meropenem, piperacillin/tazobactam.

[g] Adult studies suggest AUC:MIC is a better predictor of clinical efficacy.

[h] For example, gentamicin, tobramycin, amikacin.

[i] For example, ciprofloxacin, levofloxacin.

[j] For example, fluconazole, voriconazole.

- Pharmacodynamic characteristics are also determined from adult clinical studies (often retrospective) performed during drug development or after approval. Because adult studies often involve fixed doses and intervals, PD targets that appear to best predict outcomes in adults might not be the same in neonates, in whom doses are individualized by weight and drug clearance is much slower, yielding different concentration versus time profiles from adults. Drug-protein binding and the host immune responses can also differ. **Vancomycin** and **gentamicin** were originally identified as having time- and concentration-dependent PD characteristics, respectively. Over time, with more preclinical and clinical trial experience in adults with LRTI or sepsis, they both are now considered to also be AUC-dependent with AUC:MIC a predictor of clinical success. Neonatal PK modeling and simulation studies have determined the optimal neonatal dose to achieve the *adult*-derived AUC:MIC targets. However, too few neonatal PK/PD studies with clinical outcomes have been performed to know if the adult targets apply to the neonatal population.

Other general caveats to consider when applying the information found in the PD table to clinical care include

- Maintaining **linezolid** concentrations above MIC (time-dependent PD) is important when treating LRTI and skin infections caused by MRSA or vancomycin-resistant enterococci. Therapeutic drug monitoring may be required. Carbapenems such as **meropenem** have longer PAE against gram-negative bacilli than cephalosporins; thus, their dosing interval does not need to be as frequent. They also have a shorter percentage of time that concentrations need to be greater than MIC to be effective compared to cephalosporins.
- Toxicodynamic features of a drug can interfere with achieving its PD targets. Increasing the dose of **amphotericin B** to improve the peak concentration to MIC ratio will result in unacceptably high rates of nephrotoxicity. Treating susceptible bacteria with MICs of ≥2 mg/L with higher doses of **vancomycin** or **gentamicin** to achieve their PD targets will also lead to more nephrotoxicity. This has been recognized to occur with vancomycin in infants and children, as well as adults. Alternative agents should be chosen in such cases, even though the organism is reported as susceptible by the clinical laboratory.

C. DRUG DOSAGE TABLES

Aminoglycoside and vancomycin dosages are given in the following separate tables. See also the Individual Drug Monographs later in this chapter for more information on certain antimicrobials.

ANTIMICROBIALS

Antimicrobial	Route	Dosages (mg/kg/day) and Intervals of Administration				
		Chronologic Age ≤28 days				Chronologic Age 29–60 days
		Body Weight ≤2,000 g		Body Weight >2,000 g		
		0–7 days old	8–28 days old	0–7 days old	8–28 days old	
NOTE: This Table contains empiric dosage recommendations for each agent listed. Cross-reference chapters 3 through 6 for pathogen-specific or tissue-site dosing recommendations and for information on anti-influenza and antiretroviral drug dosages.						
Acyclovir (treatment of acute disease)	IV	60 div q8h	60 div q8h	60 div q8h	60 div q8h	60 div q8h
Acyclovir (suppression following treatment of acute disease)	PO	—	900/m^2/day div q8h	—	900/m^2/day div q8h	900/m^2/day div q8h
Amoxicillin[a]	PO	—	75 div q12h	100 div q12h	100 div q12h	100 div q12h
Amoxicillin/clavulanate[b]	PO	—	—	30 div q12h	30 div q12h	30 div q12h
Amphotericin B						
– Deoxycholate	IV	1 q24h	1 q24h	1 q24h	1 q24h	1 q24h
– Lipid complex	IV	5 q24h	5 q24h	5 q24h	5 q24h	5 q24h
– Liposomal	IV	5 q24h	5 q24h	5 q24h	5 q24h	5 q24h
Ampicillin	IV, IM	100 div q12h	150 div q12h	150 div q8h	150 div q8h	200 div q6h
Ampicillin (GBS meningitis)	IV	300 div q8h	300 div q6h	300 div q8h	300 div q6h	300 div q6h
Azithromycin	IV, PO	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
Aztreonam	IV, IM	60 div q12h	90 div q8h[c]	90 div q8h	120 div q6h	120 div q6h
Cefazolin (Enterobacteriales)[d]	IV, IM	50 div q12h	75 div q8h	100 div q12h	150 div q8h	100–150 div q6–8h
Cefazolin (MSSA)	IV, IM	50 div q12h	50 div q12h	75 div q8h	75 div q8h	75 div q8h
Cefepime	IV, IM	60 div q12h	60 div q12h	100 div q12h	100 div q12h	150 div q8h[e]
Cefotaxime	IV, IM	100 div q12h	150 div q8h	100 div q12h	150 div q6h	200 div q6h
Ceftaroline	IV, IM	12 div q12h[f]	18 div q8h[f]	18 div q8h	18 div q8h	18 div q8h

ANTIMICROBIALS

		Dosages (mg/kg/day) and Intervals of Administration				
		Chronologic Age ≤28 days				Chronologic Age 29–60 days
		Body Weight ≤2,000 g		Body Weight >2,000 g		
Antimicrobial	**Route**	**0–7 days old**	**8–28 days old**	**0–7 days old**	**8–28 days old**	
Ceftazidime	IV, IM	100 div q12h	150 div q8h[c]	100 div q12h	150 div q8h	150 div q8h
Ceftolozane/tazobactam	IV	—	—	60 div q8h	60 div q8h	60 div q8h
Ceftriaxone[g]	IV, IM	—	—	50 q24h	50 q24h	50 q24h
Ciprofloxacin[h]	IV	15 div q12h	15 div q12h	25 div q12h	25 div q12h	25 div q12h
Clindamycin	IV, IM, PO	15 div q8h	15 div q8h	21 div q8h	27 div q8h	30 div q8h
Dalbavancin	IV	22.5 once	22.5 once	22.5 once	22.5 once	22.5 once
Daptomycin (Potential neurotoxicity; use cautiously if no other options.)	IV	12 div q12h	12 div q12h	12 div q12h	12 div q12h	12 div q12h
Erythromycin	IV, PO	40 div q6h	40 div q6h	40 div q6h	40 div q6h	40 div q6h
Fluconazole						
– Treatment[i]	IV, PO	12 q24h	12 q24h	12 q24h	12 q24h	12 q24h
– Prophylaxis	IV, PO	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly
Flucytosine	PO	75 div q8h	100 div q6h[c]	100 div q6h	100 div q6h	100 div q6h
Ganciclovir	IV	12 div q12h	12 div q12h	12 div q12h	12 div q12h	12 div q12h
Linezolid	IV, PO	20 div q12h	30 div q8h	30 div q8h	30 div q8h	30 div q8h
Meropenem						
– Sepsis, IAI	IV	40 div q12h	60 div q8h[j]	60 div q8h	90 div q8h[j]	90 div q8h
– MIC 4–8 mg/L OR – Meningitis	IV	80 div q12h	120 div q8h[j]	120 div q8h	120 div q8h	120 div q8h
Metronidazole[k]	IV, PO	15 div q12h	15 div q12h	22.5 div q8h	30 div q8h	30 div q8h

Micafungin	IV	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
Nafcillin,[l] oxacillin[l]	IV, IM	50 div q12h	75 div q8h[c]	75 div q8h	100 div q6h	150 div q6h
Penicillin G benzathine	IM	50,000 U	50,000 U	50,000 U	50,000 U	50,000 U
Penicillin G crystalline (GBS meningitis)	IV	450,000 U div q8h	500,000 U div q6h	450,000 U div q8h	500,000 U div q6h	500,000 U div q6h
Penicillin G crystalline (GBS sepsis, congenital syphilis)	IV	100,000 U div q12h	150,000 U div q8h	100,000 U div q12h	150,000 U div q8h	200,000 U div q6h
Penicillin G procaine	IM	50,000 U q24h	50,000 U q24h	50,000 U q24h	50,000 U q24h	50,000 U q24h
Piperacillin/tazobactam	IV	300 div q8h	320 div q6h[m]	320 div q6h	320 div q6h	320 div q6h
Rifampin[n]	IV, PO	10 q24h	15 q24h	10 q24h	15 q24h	15 q24h
Valganciclovir	PO	Insufficient data	Insufficient data	32 div q12h	32 div q12h	32 div q12h
Voriconazole[o]	IV	8 div q12h	8 div q12h	12 div q12h	12 div q12h	16 div q12h
Zidovudine	IV	3 div q12h[p]	3 div q12h[p]	6 div q12h	6 div q12h	See Chapter 4.
	PO	4 div q12h[p]	4 div q12h[p]	8 div q12h	8 div q12h	See Chapter 4.

[a] For streptococcal and enterococcal infections.
[b] FDA-approved doses for susceptible *Haemophilus influenzae* non-CNS infections are shown in the Table. Higher dosing (75 mg/kg/day div q8h) recommended for IV to oral step-down treatment of susceptible *Escherichia coli* (MIC ≤8 mg/L). May use 25- or 50-mg/mL formulation.
[c] Use 0–7 days old dosing until 14 days old if birth weight <1,000 g.
[d] If isolate MIC 4 mg/L and no CNS focus. If MIC ≤2 mg/L can use MSSA dosing.
[e] Infuse over 3 h, or increase to 200 mg/kg/day div q6h, to treat isolates with MIC 8 mg/L.
[f] Not studied in preterm neonates. Plasma concentration monitoring recommended.
[g] Usually avoided in neonates (see Chapter 3). Can be considered for transitioning to outpatient treatment of GBS bacteremia in well-appearing neonates at low risk for hyperbilirubinemia.
[h] Oral form not studied in neonates. Consider 30–40 mg/kg/day PO div q12h as step-down therapy if completion of IV treatment course is not possible and neonate is tolerating oral feeding. The oral suspension should be administered orally and not via a feeding tube.
[i] Loading dose 25 mg/kg followed 24 h later by maintenance dose listed.
[j] Adjust dosage at 14 days of age instead of at 8 days of age.
[k] Loading dose 15 mg/kg.
[l] Double the dose for meningitis.
[m] When PMA reaches >30 wk.
[n] For either *Staphylococcus* bacteremia or primary tuberculosis.
[o] Initial loading dose of 18 mg/kg div q12h on day 1. Desired serum concentrations, trough 2–6 mg/L.
[p] Starting dose if GA <35+0 wk and PNA ≤14 days. See HIV in Chapter 4 for ZDV dosage after 2 wk of age and for discussion of other agents.

AMINOGLYCOSIDES

Empiric Dosage (mg/kg/dose) by GA and PNA

		<30 wk GA		30–34 wk GA		≥35 wk GA	
Medication	**Route**	**0–14 days**	**>14 days**	**0–10 days**	**>10 days**	**0–7 days**	**>7 days**
Amikacin	IV, IM	15 q48h	15 q24h	15 q24h	15 q24h	15 q24h	17.5 q24h
Gentamicin Tobramycin	IV, IM	5 q48h	5 q36h	5 q36h	5 q24h	4 q24h	5 q24h

VANCOMYCIN

Empiric Dosage (mg/kg/dose) by GA and SCr (Begin with a 20 mg/kg loading dose.)

	≤28 wk GA			>28 wk GA	
SCr	**Dose**	**Frequency**	**SCr**	**Dose**	**Frequency**
<0.5	15	q12h	<0.7	15	q12h
0.5–0.7	20	q24h	0.7–0.9	20	q24h
0.8–1.0	15	q24h	1.0–1.2	15	q24h
1.1–1.4	10	q24h	1.3–1.6	10	q24h
>1.4	15	q48h	>1.6	15	q48h

D. THERAPEUTIC DRUG MONITORING

Testing of blood samples for drug concentrations is occasionally required when using antimicrobials in neonates. Commonly used drugs, such as the aminoglycosides and vancomycin, and less commonly used ones, such as flucytosine and voriconazole, have target concentrations associated with their efficacy or safety. For these agents, a laboratory assay is usually readily available in the clinical setting, and routine drug concentration measurement is recommended. There are also antimicrobials used in the NICU that do not require therapeutic drug monitoring per standard of care but for which suggested target concentrations have been published. For these agents, in some situations (eg, poor response to standard dose, abnormal patient physiology), adjusting the dosage with the aid of concentration measurement in consultation with a pediatric infectious disease specialist may improve care. The following Table provides guidance on concentration targets for routinely and seldomly monitored antimicrobials used in neonates.

Drug	Target[a] (mg/L)	Comment
Acyclovir[b]	Trough >1 (efficacy) Peak <50 (safety)	Efficacy target = T>IC_{50} Safety = neurotoxicity
Amikacin	Trough <7 (safety) Peak 20–35 (efficacy)	Efficacy target = 10•MIC Safety = nephrotoxicity
Amphotericin B	Peak 2–4 (efficacy)	Efficacy target = 4•MIC
Ceftaroline[b]	>1 at 60% of the dosing interval (5–6 h post-dose for q8h interval) (efficacy)	MIC 0.5 or 1 mg/L for MRSA No known concentration-dependent toxicity, but neutropenia associated with long-term use.
Fluconazole[b]	AUC_{24}/MIC 50–100 mg•h/L (efficacy)	Trough of 15–20 mg/L is a reasonable proxy when AUC calculation is not possible.
Flucytosine[b]	Trough 10–20 (efficacy) Peak 60–80 (<100) (safety)	Efficacy target = T>MIC for *Cryptococcus*. Lower trough target of 5–10 and %T>MIC 40% acceptable for invasive candidiasis. Safety = neutropenia
Ganciclovir[b]	AUC_{12} 27 mg•h/L (efficacy) Range 23–36 mg•h/L	No known safety target[c]
Gentamicin[d]	Trough <2 (safety) Peak 6–12 (efficacy)	Efficacy target = 10•MIC Safety = nephrotoxicity
Linezolid[b]	Trough ≥2 (efficacy) Trough <9 (safety)	Safety = thrombocytopenia
Meropenem	>8 at 70% of the dosing interval (8 h post-dose for q12h interval) (efficacy)	Assuming isolate MIC 4–8 mg/L and using higher dose. Should not need plasma concentration monitoring for susceptible isolate MIC ≤2 mg/L.
Vancomycin	Trough 8–12 (efficacy)[e] Trough <15 (safety)	15–25 for continuous infusion Safety = nephrotoxicity
Voriconazole	Trough 2–6 (efficacy)	Safety target not well established. Maintaining concentrations in efficacy target range should minimize side effects.

[a] Serum or plasma concentration at steady state.
[b] May not be routinely clinically available at all centers.
[c] Hematologic toxicity possible at therapeutic doses.
[d] The same targets apply to tobramycin.
[e] High probability of achieving AUC_{24} ≥400 in neonates.

Considerations for therapeutic drug monitoring in the NICU

- Empiric treatment for suspected early- or late-onset sepsis is often discontinued after 36–48 hours (see Chapter 7). Postponing therapeutic drug monitoring of aminoglycosides or vancomycin until after 48 hours if treatment is continued is reasonable to avoid unnecessary laboratory testing. Exceptions would be when altered PK is suspected (eg, AKI, hypotension, patent ductus arteriosus treatment, extracorporeal membrane oxygenation), or there is microbiologic confirmation of infection. Early

therapeutic drug monitoring should also be at the discretion of the treatment team if bacterial infection is strongly suspected based on maternal/birth history and/or clinical presentation.

- When aminoglycosides are used for synergy, trough monitoring is sufficient.
- Neonatal PK model-informed Bayesian-feedback software tools are preferred for analyzing measured concentrations. Sawchuk-Zaske PK calculation tools are also acceptable.
- Area under the concentration-time curve during a 24-hour dosing period can be estimated by using the following formula: Total Daily Dose (mg)/Clearance (L/h).
- Be judicious with blood sampling to avoid contributing to phlebotomy anemia and NEC.
  - Neonatal total blood volume is approximately 80 mL/kg. A 600-g neonate has a total blood volume of only 48 mL. A peak and trough, 1 mL each, represents 4% of total blood volume.
  - Time therapeutic drug monitoring samples to occur with other routine blood draws whenever possible to minimize blood waste, to prevent additional painful blood drawing procedures, and to be respectful of nursing time.
  - PK software equipped with Bayesian estimation tools based on neonatal population PK models can help predict peak and trough values and AUC when sampling is sparse.
- Know your limits.
  - Treating an isolate with MIC $\geq$2 will require very high doses of gentamicin or vancomycin ($\geq$8 for amikacin) to achieve target concentrations, and toxicity is more likely at these concentrations. Use an alternative agent (see Chapter 3).
  - If the antimicrobial has poor penetration to or activity at the site of infection (eg, central nervous system or intra-abdominal abscess for gentamicin or vancomycin), achieving target blood concentrations may be of little value. Use an alternative agent (see Chapter 3).
- Treat the patient, not the number.
  - If the neonate has microbiological cure and clinical improvement despite not achieving target concentrations, it is still a win. Adjust the dose to prevent a potential relapse from subtherapeutic concentrations, but do not keep sampling, analyzing, and dose adjusting just to make the PK numbers the best they can possibly be.
  - If a measured concentration does not make sense or is not consistent with the patient's physiology, there might have been a dose administration or sampling error. Administration of small drug volumes in neonates is known to be unreliable depending on the technique and equipment used. Repeat the measurement instead of dose adjusting based on a spurious value.

E. INDIVIDUAL DRUG MONOGRAPHS

Acyclovir

Administered: IV, PO **Excreted: Renally**

Acyclovir is a deoxyguanosine analog antiviral effective against HSV types 1 and 2. It is less active but effective against VZV and not effective against CMV.

Pharmacodynamics: Time above IC_{50}

Susceptible Isolate IC_{50}: HSV (types 1 and 2) 0.56 mg/L; VZV 1.125 mg/L

Dosing

- Acute Neonatal HSV Infection: 20 mg/kg/dose IV every 8 hours
  - 20 mg/kg every 12 hours if PMA <30 weeks.
  - 20 mg/kg every 24 hours with AKI stage 1 or greater
  - Only IV acyclovir should be used for the treatment of acute neonatal HSV disease
- HSV Suppressive Therapy (post-IV therapy): 300 mg/m²/dose PO every 8 hours
  - Use Haycock or Mosteller BSA formula.
  - Oral therapy for 6 months' duration after completion of initial IV treatment (see Chapter 4).
- VZV: 20 mg/kg/dose IV every 8 hours
- Post-VZV Exposure Prophylaxis: 20 mg/kg/dose PO every 6 hours (if VZIG unavailable)

  Can also be considered for HSV prophylaxis after iatrogenic or visitor exposure while awaiting diagnostic results if infant is asymptomatic

Formulations and Administration

- Dilute the 50 mg/mL concentrated solution to ≤7 mg/mL in D5W or physiologic (normal) saline prior to IV administration. Administer slowly over at least 1 hour.
- 40 mg/mL oral suspension (commercially available), banana flavored.

Main Toxicities: nephrotoxicity, neutropenia

- Obstructive nephropathy and AKI can be caused by formation and precipitation of acyclovir crystals in renal tubules. Risk factors include rapid IV infusion, overdose, concomitant nephrotoxic drugs (eg, amphotericin B, gentamicin, vancomycin), dehydration, mechanical ventilation, and preexisting renal dysfunction. Monitor urine output and SCr.
- Severe phlebitis and cutaneous necrosis can occur with extravasation.

Amphotericin B

Administered: IV **Excreted: Renally, Fecally**

Amphotericin B is a polyene broad-spectrum antifungal, active against yeast and molds such as *Candida albicans* and non-*albicans* species (although resistance is more prevalent with *C lusitaniae* and *C auris*), *Aspergillus, Cryptococcus, Histoplasma, Coccidioides, Blastomyces, Mucor,* and other *Zygomycetes,* and the protozoan parasite *Leishmania.* Amphotericin B and fluconazole have better renal and CNS distribution than echinocandins (eg, micafungin) and are the preferred first-line agents to treat neonatal invasive candidiasis.

Pharmacodynamics: Peak (2 h after end of infusion)/MIC ratio 4:1

Susceptible Isolate MICs: *Candida* ≤1 mg/L, *Aspergillus* ≤0.5 mg/L

Neonatal and Infant Dosing

- Amphotericin B Deoxycholate: 1 mg/kg every 24 hours.
- Amphotericin B Liposomal OR Lipid Complex: 5 mg/kg every 24 hours. May increase to 7 mg/kg if needed to achieve microbiological eradication.

Formulations and Administration: All formulations are incompatible with saline, including saline flush.

- Amphotericin B Deoxycholate: Reconstitute with sterile water to 5 mg/mL, then further dilution with D5W to 0.1 mg/mL for peripheral-venous catheter administration or with dextrose between 5% and 20% to 0.5 mg/mL maximum concentration for central-venous catheter administration. Infuse over at least 2 hours. Filtering to prevent phlebitis is not necessary. If an in-line filter is used, the pore size should be >1 μm to prevent drug retention in the filter.
- Amphotericin B Liposomal: Reconstitute with sterile water to 4 mg/mL, then filter (5 μm) and dilute to 1 or 2 mg/mL with dextrose between 5% and 20% and infuse over 1 hour. If an in-line filter is used, the pore size should be >1 μm.
- Amphotericin B Lipid Complex: Filter (5 μm), then dilute to 1 or 2 mg/mL with D5W and infuse over 2 hours. Do not use an in-line filter.

Lipid-based amphotericin formulations were developed to improve systemic tolerability (less chills/fevers and nephrotoxicity) over the deoxycholate form when treating invasive fungal infections in cancer or other immunocompromised adult and pediatric patients. This safety advantage allows lipid-based amphotericin formulations to be given in higher doses than the deoxycholate form, which improves their efficacy.

There are no prospective trials comparing the effects of deoxycholate and lipid-based formulations in neonates. The body of available data from retrospective and observational studies does not indicate that one formulation is definitively more effective or less safe than the other. Both formulations are likely to be effective in treating susceptible fungal meningitis. Unlike in older children and adults, neonates do not experience higher rates

of infusion reactions and nephrotoxicity with amphotericin B deoxycholate compared with lipid formulations. If unsuccessful treatment, renal toxicity, or infusion reaction occurs in a neonate receiving the deoxycholate formulation, it is reasonable to switch to a lipid formulation.

Key Advantages of Each Formulation

- Deoxycholate: more PK and clinical data and historical use in neonates, higher renal tissue distribution.
- Lipid: less infusion volume, better lung and liver penetration. Liposomal form also has shorter infusion time and can push dose to 7 mg/kg without increasing adverse effects.

Main Toxicities: kidney injury, hypokalemia, elevated transaminases, anemia, thrombocytopenia

Ampicillin

Administered: IV, IM **Excreted: Renally**

Ampicillin is a beta-lactam aminopenicillin antibacterial that is effective against GBS, *Listeria,* and most strains of *Enterococcus.* It may have efficacy against certain gram-negative bacteria, but resistance is common, including among *Escherichia coli* and *Klebsiella*.

Pharmacodynamics: Time above MIC; maintain concentrations above MIC.

Susceptible Isolate MICs: GBS <0.5 mg/L, *Listeria* ≤2 mg/L, *Enterococcus* and *E coli* ≤8 mg/L

Neonatal Dosing[a]

GA ≤34 wk		GA >34 wk	
PNA ≤7 days	PNA 8–28 days	PNA ≤7 days	PNA 8–28 days
50 mg/kg q12h	75 mg/kg q12h	50 mg/kg q8h	50 mg/kg q8h

Given dosages should achieve trough concentration ≥8 mg/L, which is 16-times above GBS MIC.

[a] GBS meningitis dosing is 100 mg/kg/dose every 8 hours (if age ≤7 days) or every 6 hours (if age >7 days) regardless of GA.

Infant Dosing (>1 mo): 50 mg/kg/dose every 6 hours

Formulations and Administration

- 100 mg/mL diluted in sterile water for direct IV administration. Infuse over 3 to 5 minutes.
- 250 mg/mL in sterile water for IM administration.

Do not mix with gentamicin in the same tubing or syringe; mutual partial inactivation may result.

Main Toxicities: usually well tolerated

Cefazolin

Administered: IV, IM **Excreted: Renally**

Cefazolin is a first-generation beta-lactam cephalosporin antibacterial effective against oxacillin-susceptible *Staphylococcus*, streptococci, and some gram-negative bacilli such as *Escherichia coli* and *Klebsiella* species but not *Enterobacter or Serratia* species. Cefazolin is not active against *Pseudomonas, Acinetobacter, Enterococcus,* or beta-lactamase–positive anaerobes.

Pharmacodynamics: Time above MIC

Susceptible Isolate MICs: *S aureus,* gram-negative bacilli ≤2 mg/L

Neonatal Dosing[a]

Weight ≤2 kg		Weight >2 kg	
PNA ≤7 days	PNA >7 days	PNA ≤7 days	PNA >7 days
25 mg/kg q12h	25 mg/kg q12h	25 mg/kg q8h	50 mg/kg q8h

For treating gram-negative bacilli bloodstream infections with an MIC of 4 or 8 mg/L

Weight ≤2 kg		Weight >2 kg	
PNA ≤7 days	PNA >7 days	PNA ≤7 days	PNA >7 days
25 mg/kg q12h	25 mg/kg q8h	50 mg/kg q12h	50 mg/kg q8h

[a] The recommendations in the lower dosing table are designed to achieve unbound serum concentrations >8 mg/L for 60% of the dosing interval. The clinical laboratory will report gram-negative bacilli from blood cultures with an MIC of 4 mg/L as "intermediately susceptible" based on adult PK/PD assumptions.

Infant Dosing (>1 mo): 50 mg/kg every 8 hours or 25 mg/kg every 6 hours

Surgical Prophylaxis: 30 mg/kg given 30 to <60 minutes prior to skin incision

Cardiopulmonary Bypass: Give additional 15 mg/kg at start and at rewarming. Begin postoperative prophylaxis 30 mg/kg at 8 hours after intraoperative rewarming dose.

Formulations and Administration

- IV: 100 mg/mL reconstituted and diluted in sterile water. Administer over 30 minutes (range 5–45 minutes).
- IM: 225 mg/mL reconstituted with sterile water.

Main Toxicities: usually well tolerated in neonates

Cefepime

Administered: IV, IM* **Excreted: Renally**

Cefepime is a beta-lactam cephalosporin used for its activity against gram-negative bacilli, particularly *Pseudomonas aeruginosa* and organisms that commonly produce inducible chromosomal ampC beta-lactamase such as *Enterobacter cloacae, Citrobacter freundii, and Klebsiella aerogenes.* It may also be used for commonly encountered non-inducible, ampC-producing, gram-negative bacilli such as *Escherchia coli*, other Klebsiella species, and *Serratia marcescens.* It has good activity against streptococci, *Neisseria, Haemophilus influenzae,* and oxacillin-susceptible *Staphylococcus aureus,* although narrower spectrum agents are typically used against these pathogens. Cefepime is not active against *Enterococcus* or beta-lactamase–positive anaerobes.

Pharmacodynamics: Time above MIC

Susceptible Isolate MICs: *Pseudomonas* ≤8 mg/L, Enterobacteriales ≤2 mg/L, *Streptococcus* (beta-hemolytic) ≤0.5 mg/L

Neonatal Dosing[a]

GA <36 wk	GA ≥36 wk
30 mg/kg q12h	50 mg/kg q12h[b]

[a] The recommendations in the dosing table are designed to achieve serum concentrations of at least 8 mg/L for 60% of the dosing interval. The clinical laboratory will report Enterobacteriales with an MIC of 4–8 mg/L as "susceptible dose-dependent" based on adult PK/PD assumptions. Such organisms would be expected to be susceptible to cefepime if given according to doses in the table.

[b] A lower dose of 30 mg/kg q12h is appropriate for susceptible *E coli* or other Enterobacteriales.

Infant Dosing (>1 mo): 50 mg/kg every 8 hours. May require 50 mg/kg every 6 hours to treat organisms with MIC of 8 mg/L.

Formulations and Administration

- IV: 100 mg/mL reconstituted and diluted in sterile water. Administer over 30 minutes.
- IM: 280 mg/mL reconstituted with sterile water.

Cefepime has been prospectively studied and shown to be effective for pediatric meningitis. Cefepime is, therefore, appropriate for neonates with bacteremia in situations where antibiotic diffusion into spinal fluid would be desirable. For documented bacterial meningitis, other, better studied agents should be used.

Main Toxicities: usually well tolerated in neonates. Rare side effects (<5%): thrombocytopenia, hyperkalemia, seizures. Use of broad-spectrum agents such as cefepime enriches drug-resistant genes in the neonatal fecal microbiome, and in very low birth weight neonates it is associated with an increased risk of candidiasis, similar to other broad-spectrum therapy (see Chapter 7).

*Cefepime given IM is not well studied in neonates. Serum concentrations may be lower and susceptible dose-dependent organism treatment failure risk may be increased.

Cefotaxime

Administered: IV, IM **Excreted: Renally**

Cefotaxime is a beta-lactam cephalosporin antibacterial effective against Enterobacteriaceae, *Haemophilus influenzae, Neisseria, Streptococcus,* and methicillin-susceptible *Staphylococcus aureus.* Cefotaxime is not active against *Pseudomonas, Acinetobacter, Enterococcus,* or anaerobes. Treatment failure is possible when cefotaxime is used to treat chromosomal ampC beta-lactamase–producing gram-negative bacilli (see Cefepime Individual Drug Monograph).

Pharmacodynamics: Time above MIC

Susceptible Isolate MIC: ≤1 mg/L

Neonatal Dosing[a]

GA <32 wk		GA ≥32 wk	
PNA <7 days	PNA ≥7 days	PNA ≤7 days	PNA >7 days
50 mg/kg q12h	50 mg/kg q8h	50 mg/kg q12h	50 mg/kg q6h

[a] The recommendations in the dosing table are designed to achieve concentrations >MIC for 75% of the dosing interval when the MIC is ≤2 mg/L during the first week after birth and ≤4 mg/L in the second week after birth. This is to account for covering *Klebsiella* species that are more frequently isolated in late-onset neonatal infections and can have MICs of 2–4 mg/L. The clinical laboratory will report Enterobacteriales with an MIC of 2 mg/L as "intermediately susceptible" based on adult PK/PD assumptions.

Formulation and Administration

- IV: 100 mg/mL reconstituted and diluted in sterile water. Administer over 30 minutes (range 5–45 minutes). Avoid rapid administration.
- IM: 300 mg/mL reconstituted with sterile water.

Main Toxicities: usually well tolerated in neonates. Use of broad-spectrum agents such as cefotaxime enriches drug-resistant genes in the neonatal fecal microbiome, and in very low birth weight neonates it is associated with an increased risk of candidiasis as with other broad-spectrum therapy (see Chapter 7).

Ceftazidime

Administered: IV, IM **Excreted: Renally**

Ceftazidime is a beta-lactam cephalosporin used for its activity against gram-negative bacilli, particularly *Pseudomonas aeruginosa*, when treating neonatal sepsis and meningitis. Ceftazidime is not stable against inducible chromosomal ampC beta-lactamases or extended-spectrum beta-lactamases, so cefepime or meropenem are preferred to treat gram-negative bacteria with these resistance factors. Although ceftazidime is not a typical anti-gonococcal cephalosporin, it does have activity against *Neisseria gonorrhoeae* and may be used in place of ceftriaxone if contraindicated. Ceftazidime has poor activity against *Streptococcus pneumoniae*, viridans streptococci, and *Staphylococcus aureus* compared with cefotaxime, ceftriaxone, and cefepime, which gives it a reputation as a weak performer against gram-positive bacteria. However, it is active and should be effective against group A and B streptococcal infections, although narrower-spectrum agents such as penicillin or ampicillin are preferred. Most gut flora anaerobes are resistant to ceftazidime due to extensive beta-lactamase production. Like other cephalosporins, ceftazidime is not active against *Enterococcus* or *Listeria*.

Pharmacodynamics: Time above MIC

Susceptible Isolate MICs: Pseudomonas ≤8 mg/L, Enterobacteriales ≤4 mg/L

Neonatal Dosing[a]

GA <32 wk		GA ≥32 wk	
PNA ≤14 days	PNA >14 days	PNA ≤7 days	PNA >7 days
25 mg/kg q12h	25 mg/kg q8h	25 mg/kg q12h	25 mg/kg q8h

[a] The recommendations in the dosing table are designed to empirically treat *Escherichia coli* and other susceptible, non-ampC beta-lactamase–producing Enterobacteriales. Increase dose to 50 mg/kg if treating suspected or confirmed meningitis. If targeting *Pseudomonas*, increase the dose to 50 mg/kg and combine with tobramycin (see Chapter 3).

Infant Dosing (>1 mo): 50 mg/kg every 8 hours. May require every 6 hours to treat *Pseudomonas* isolates with MIC of 8 mg/L.

Formulations and Administration

- IV: 100 mg/mL reconstituted and diluted in sterile water. Administer over 30 minutes.
- IM: 280 mg/mL reconstituted with sterile water.

Main Toxicities: usually well tolerated in neonates and infants. Rare side effects (<5%): thrombocytopenia, hyperkalemia, seizures. Use of broad-spectrum agents such as cefepime enriches drug-resistant genes in the neonatal fecal microbiome, and in very low birth weight neonates it is associated with an increased risk of candidiasis, similar to other broad-spectrum therapy (see Chapter 7).

Fluconazole

Administered: IV, PO **Excreted: Renally**

Fluconazole is a triazole antifungal effective against *Candida albicans* and the non-*albicans* species *C lusitaniae, C parapsilosis,* and *C tropicalis.* The species *C krusei* is inherently resistant to fluconazole, and *C auris* resistance is very high (>90%). Resistance to *C glabrata* is high enough in some centers and regions such that fluconazole should not be used to treat *C glabrata* infection unless susceptibility is confirmed. Although fluconazole is active against *Cryptococcus,* the effective dosage is not known for neonates and is likely much higher than that used for treating candidiasis. The combination of amphotericin B and flucytosine is preferred. Fluconazole is not used to treat *Aspergillus* infections due to weak activity and resistance.

Pharmacodynamics: AUC:MIC; target ratio >50 (400 mg•h/L AUC to 8 mg/L MIC).

Susceptible Isolate MICs: *C albicans* ≤8 mg/L

Neonatal and Infant *Candida* Treatment Dosing (up to 90 days of age): 25 mg/kg loading dose followed in 24 hours with 12 mg/kg every 24 hours

- For neonates receiving ECMO, loading dose should be 35 mg/kg.
- Consider reducing maintenance dose by 50% if serum creatinine is >1.2 mg/dL.
- Consider 20 mg/kg every 24 hours maintenance dose in PMA neonates ≥30 weeks if there is an inadequate clinical or microbiologic response.
- 6 mg/kg PO/IV every 24 hours for oral thrush.

Neonatal and Infant *Candida* Prophylaxis Dosing (up to 80 days of age):
3 or 6 mg/kg IV every 72 hours in preterm neonates <30 weeks' GA

- Change to 6 mg/kg every 48 hours once >42 days' PNA.
- Change to 6 mg/kg once weekly if serum creatinine is >1.2 mg/dL.
- 6 mg/kg every 48 hours starting dosage for preterm neonates ≥30 weeks' GA.

Formulations and Administration

- 2 mg/mL premade parenteral solution for IV use. Infuse loading dose over 2 hours and maintenance dose over 1 hour.
- 50 mg/5 mL and 200 mg/5 mL oral suspension. May give with feedings.

Main Toxicities: usually well tolerated. Reversible modest increases in hepatic transaminases occur occasionally.

In adult and in vitro studies, fluconazole interacts with and decreases the clearance of fentanyl, midazolam, and methadone, increasing the risk of respiratory depression, excessive sedation, and QTc prolongation. The hepatic CYP isoform responsible for this interaction is not developmentally expressed at birth and typically only becomes significantly active after 3 months after birth, possibly sooner in formula-fed infants. These interactions may therefore not be relevant in the NICU. Clinical monitoring for exaggerated effect is reasonable and prudent when fluconazole is used concomitantly with these agents.

Gentamicin

Administered: IV, IM **Excreted: Renally**

Gentamicin is an aminoglycoside antibacterial with activity against many gram-negative bacilli. Compared with tobramycin, gentamicin has better activity against *Serratia* but is less active against *Pseudomonas aeruginosa.* It is also synergistically active against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus agalactiae* (GBS), viridans streptococci, and *Enterococcus* when given in combination with a penicillin or glycopeptide antibiotic. Gentamicin is not active against anaerobes or against facultative anaerobes infecting an abscess or necrotic tissue.

Pharmacodynamics: Peak to MIC ratio, goal ratio ≥10

Susceptible Isolate MICs: gram-negative bacilli ≤2 mg/L. *Enterococcus* and viridans streptococci MIC ≤128 mg/L reported by the clinical laboratory indicates low-level intrinsic resistance and gentamicin can be used synergistically.

Neonatal Dosing (mg/kg/dose)

<30 wk GA		30–34 wk GA		≥35 wk GA	
0–14 days	>14 days	0–10 days	>10 days	0–7 days	>7 days
5 q48h	5 q36h	5 q36h	5 q24h	4 q24h	5 q24h

Alternative Early-Onset Sepsis Dosing: 7.5 mg/kg every 48 hours for all neonates to improve the probability of achieving peak concentration ≥10 mg/L (IQR 15–20 mg/L) after the first dose while maintaining a trough ≤2 mg/L. Such a strategy might be useful in centers where early-onset sepsis caused by *Escherichia coli* with MICs 1–2 mg/L is not uncommon.

Formulation and Administration: 10 mg/mL "pediatric" strength; may be used undiluted for IV or IM administration. Infuse IV over 20–30 minutes. Do not co-infuse with piperacillin/tazobactam.

Concomitant treatment with indomethacin or ibuprofen can reduce gentamicin clearance.

Main Toxicities

- Nephrotoxicity. Risk is assumed to be increased when trough concentrations are 2 mg/L based on adult data. However, nephrotoxicity incidence is rare and no different compared with other agents in neonatal clinical studies. Nephrotoxicity has also not been reported in clinical studies comparing gentamicin dosing regimens. The apparent lack of nephrotoxicity may be due to nephron immaturity and reduced renal tubular uptake. In adults, high-dose, AUC-targeted regimens cause more nephrotoxicity when the daily dose is divided and troughs are 1–2 mg/L. Such regimens are not widely used or clinically studied in neonates. Clinicians should be cautious of potential kidney injury if adopting such regimens in the NICU.

- Ototoxicity. Aminoglycosides are ototoxic drugs, but ototoxicity is uncommon in neonatal clinical trials (<5%) and has not been linked to serum concentration or length of therapy. Epidemiologic studies have also not found neonatal aminoglycoside exposure to be an independent risk factor. In children and adults, ototoxicity is related to duration of therapy (eg, lengthy regimens for tuberculosis or repeated regimens for cystic fibrosis).

  Gentamicin may be a co–risk factor for ototoxicity in some neonates with one of the following:

  - HIE/TH and trough concentrations >2 mg/L
  - Coadministration with >7-day courses of loop diuretics
  - Mitochondrial 12S rRNA *MT-RNR1* gene mutation
  - Excess NICU noise
  - Neuromuscular paralysis can occur when certain risk factors are present, such as serious hypermagnesemia (>4 mg/dL) or concurrent neuromuscular disease such as botulism.

Meropenem

Administered: IV **Excreted: Renally**

Meropenem is a beta-lactam carbapenem antibacterial effective against *Pseudomonas,* Enterobacteriaceae (including ampC beta-lactamase–producing isolates and extended-spectrum beta-lactamase–producing *Escherichia coli* and *Klebsiella* species), and most clinically important anaerobes, including beta-lactamase–producing *Bacteroides* and *Prevotella.* Meropenem is also active against streptococci groups A, B, C, G, F, and viridans streptococci; *Streptococcus pneumoniae;* and oxacillin/methicillin-susceptible *Staphylococcus aureus;* however, narrower-spectrum agents are more appropriate for infections caused by these gram-positive pathogens. Meropenem has reduced activity against *Enterococcus faecalis* and is not effective against MRSA or *Enterococcus faecium.* In the NICU, meropenem is an appropriate choice to treat ESBL infections, *Pseudomonas* infections, gram-negative bacilli meningitis, and mixed aerobic/anaerobic infections, such as omphalitis/necrotizing fasciitis, or intra-abdominal infections, such as NEC.

Pharmacodynamics: Time above MIC

Susceptible Isolate MICs: Enterobacteriales ≤1 mg/L, *Pseudomonas aeruginosa* ≤2 mg/L

Neonatal Dosing (up to 90 days of age)[a,b]

GA <32 wk		GA ≥32 wk	
PNA <14 days	PNA ≥14 days	PNA <14 days	PNA ≥14 days
20 mg/kg q12h	20 mg/kg q8h	20 mg/kg q8h	30 mg/kg q8h

[a] The recommendations in the dosing table are designed to achieve plasma concentrations >2 mg/L for 75% of the dosing interval and >4 mg/L for 50% of the dose interval.

[b] For meningitis due to susceptible organisms, or for non-CNS infections due to isolates with MICs of 4 or 8 mg/L, use 40 mg/kg/dose in this table.

Formulations and Administration

- 20 mg/mL by first reconstituting with sterile water to 50 mg/mL, then diluting with physiologic (normal) saline. Infuse over 30 minutes. May also give over 1–5 minutes if needed to avoid incompatibilities.
- Extended infusion over 2–4 hours or continuous infusions (eg, 20 mg/kg over 8 hours every 8 hours) increase the % of time that plasma concentrations are >2 mcg/L and >4 mcg/L and may be a potentially better strategy than bolus or 30-minute infusion in treating serious infections caused by organisms with meropenem MIC values of 4–8 mcg/mL. However, CSF concentrations are not similarly improved and may be slightly decreased with extended or continuous meropenem infusions in neonates.

Main Toxicities: usually well tolerated. May (<5% incidence) cause diarrhea, oral or diaper candidiasis, glossitis, fungal sepsis, elevated hepatic transaminases, and leukopenia. Use of broad-spectrum agents such as meropenem enriches drug-resistant genes in the neonatal fecal microbiome, and in very low birth weight neonates it may increase the risk of candidiasis as with other broad-spectrum therapy (see Chapter 7).

Micafungin

Administered: IV **Excreted: Hepatobiliary**

Micafungin is an echinocandin antifungal used as a second-line agent for invasive candidiasis when neonatal first-line agents, amphotericin B or fluconazole, are not options due to resistance, toxicity, or insufficient clinical response. Because micafungin is minimally eliminated renally with very low concentrations documented in the urine of adults, candidiasis guidelines have traditionally recommended against treating urinary tract *Candida* infections with micafungin or other echinocandins. However, renal tissue levels of micafungin should be sufficient to treat azole-resistant non-*albicans Candida* infections in the upper urinary tract and, therefore, is worth a try if amphotericin B is not feasible or contraindicated. Micafungin may also be used as combination therapy with voriconazole for invasive aspergillosis but not as monotherapy (see Chapter 5).

Pharmacodynamics (*Candida* infections): concentration-dependent, ratio of AUC:MIC

Susceptible Isolate MICs (mg/L): *C glabrata* ≤0.06; *C albicans* and *C krusei* ≤0.25; *C parapsilosis* ≤2

Neonatal and Infant Dosing (up to 4 mo): 10 mg/kg IV every 24 hours

- A higher dose of 15 mg/kg may be considered in CNS infection that is not responding to initial treatment. Consultation with a pediatric infectious disease specialist is recommended.
- An AUC target of 170 mg·h/L and an AUC:MIC target of 1,332 for CNS infection have been suggested based on a rabbit model of hematogenous *Candida* meningoencephalitis. 10 mg/kg q24h dosing achieves this level of exposure in most neonates and young infants, but evidence of improved clinical outcomes is lacking. 8 mg/kg q24h has demonstrated clinical efficacy in neonates with invasive candidiasis, including some with CNS infection. The "optimal" dose is likely somewhere in the 8–15 mg/kg range.
- Plasma concentrations are slightly elevated in adults with severe hepatic dysfunction due to cirrhosis but have not been evaluated in patients with PNAC. Consider lowering the dose to 8 mg/kg in neonates with PNAC, assuming some impairment of micafungin excretion.
- 4 mg/kg IV q24h is adequate for CLABSI-associated candidemia with adequate source control if CNS infection has been excluded.

Formulations and Administration

- IV: 1 mg/mL; reconstitute a 50-mg vial with 5 mL physiologic (normal) saline or D5W to create a 10 mg/mL solution, then dilute further with 45 mL of the same solution used to reconstitute to create a final 1 mg/mL (50 mg/50 mL) product.
- An up to 4 mg/mL final product may be prepared if needed for fluid restriction. The manufacturer recommends infusing concentrations >1.5 mg/mL through a central venous catheter to avoid phlebitis due to the acidity of solution at concentrations >1.5 mg/mL despite it being iso-osmolar.
- Administer over 60 minutes. Monitor closely for phlebitis, vasodilation, and rash.

Main Toxicities: transient elevation of liver transaminases >3 times ULN and total hyperbilirubinemia >2 times ULN are common findings in most neonatal studies. Monitor liver function blood tests and consider discontinuation if values remain persistently elevated. Phlebitis and local infusion reactions (swelling, flushing, rash) are rarely reported (<1%) in neonatal studies but are more commonly reported in adults.

Nafcillin OR Oxacillin

Administered: IV/IM **Excreted: Nafcillin, Hepatobiliary; Oxacillin, Renally**

Nafcillin and oxacillin are narrow-spectrum, semisynthetic penicillins designed for resistance to staphylococcal penicillinase. Their sole use is for treatment of penicillin-resistant, oxacillin-susceptible *Staphylococcus aureus* bloodstream or focal infections. They may be active against other gram-positive pathogens such as GBS, *Listeria,* and *Enterococcus;* however, ampicillin and penicillin are better studied and should be used instead. They are not active against anaerobes or gram-negative bacteria. Like most other beta-lactams, they are not effective against MRSA due to poor affinity for the organism's unique penicillin-binding protein 2a, encoded by the *mecA* gene. Most coagulase-negative staphylococci in health care settings have acquired the same *mecA* mechanism of resistance to nafcillin and oxacillin.

Like other penicillins, their CNS penetration is poor but increases somewhat in meningitis.

Quality evidence supporting neonatal dosing is lacking, although both are FDA approved for neonates.

Pharmacodynamics: Time above MIC

Susceptible Isolate MIC: *S aureus* ≤2 mg/L

Neonatal Dosing (0–30 DOL)[a]

GA ≤34 wk		GA >34 wk	
PNA ≤7 days	PNA >7 days	PNA ≤7 days	PNA >7 days
25 mg/kg q12h	25 mg/kg q8h	25 mg/kg q8h	25 mg/kg q6h

[a] Recommendations differ from FDA-approved dosing. Increase the dose to 50 mg/kg IV when treating meningitis.

Infant Dosing (>1 mo): 37.5 mg/kg q6h (up to 50 mg/kg IV q4h for meningitis)

Formulation and Administration

- IV: Reconstitute 1 g vial with 9.3 mL (nafcillin) or 10 mL (oxacillin) of sterile water for a final concentration of 100 mg/mL. Infuse over 10–30 minutes. Can consider administering total daily dose as a continuous IV infusion when treating meningitis if inadequate clinical response or improvement in CSF indices.
- IM: Reconstitute 1 g nafcillin vial with 3.4 mL of sterile water for a final concentration of 250 mg/mL. Reconstitute 1 g oxacillin vial with 5.4 mL of sterile water for a final concentration of 167 mg/mL.

Main Toxicities

- Both can cause serious extravasation injury. Closely monitor for this side effect during infusion and treat promptly with hyaluronidase if it does occur.
- Elevated hepatic transaminases and neutropenia have been observed in pediatric studies of both agents. Monitoring for these side effects would be prudent with long-term dosing (eg, >10 days).

Penicillin G

Administered: IV, IM **Excreted: Renally**

Penicillin is a beta-lactam natural penicillin antibacterial effective against the gram-positive pathogens GBS (*Streptococcus agalactiae*), group A *Streptococcus* (*S pyogenes*), the *viridans* group of streptococci, and the Spirochaetaceae *Treponema pallidum,* which causes syphilis, and *Borrelia burgdorferi,* which causes Lyme disease. *Listeria* and most *Enterococcus faecalis* are susceptible to penicillin, but ampicillin is preferred for both organisms (see Chapter 3).

- Although penicillin and ampicillin MICs have traditionally been similar for *Listeria monocytogenes* and the 2 agents are used interchangeably throughout the world, more clinical experience in the Unites States with ampicillin, particularly in pregnancy, has led to it being the drug of choice for *Listeria* treatment.
- Ampicillin has better activity against *Enterococcus*, and therapeutic concentrations can be achieved with standard ampicillin dosing; thus, ampicillin is generally preferred.

Penicillin resistance among *bovis* and *milleri* group of *Streptococcus* is increasing. Staphylococci are usually resistant to penicillin due to a beta-lactamase. *Neisseria* species may also be resistant due to the presence of a beta-lactamase. However, if culture results demonstrate susceptibility to these organisms, penicillin should be effective.

Most sepsis-causing gram-negative bacilli and beta-lactamase–positive anaerobes *Bacteroides* and *Prevotella,* which cause intra-abdominal and head/neck infections, are resistant to penicillin.

Pharmacodynamics: Time above MIC

Susceptible Isolate MICs: *S agalactiae* $\leq$0.12 mg/L, *Enterococcus* $\leq$8 mg/L, *N gonorrhoeae* $<$2 mg/L (or beta-lactamase negative)

Neonatal Dosing

- Penicillin G K^+ or Na^+ (aqueous penicillin)

All GA	
PNA 1–7 days	PNA $\geq$8 days
50,000 units/kg/dose q12h[a]	50,000 units/kg/dose q8h

[a] Dosage is highly likely to achieve serum concentrations of at least 2 mg/L for 40% of the dosing interval in all neonates and for 100% of the dosing interval in preterm neonates $<$32 weeks' GA. Neonatal penicillin PK are not well studied beyond the first postnatal week.

- GBS Meningitis: 125,000 units/kg/dose every 6 hours for all GA and PNA; due to the very short half-life of penicillin in neonates $>$7 days, ampicillin is preferred for confirmed GBS meningitis (see Chapter 3).
- Penicillin G Procaine Injection Suspension (use only for congenital syphilis): 50,000 units/kg, **IM route ONLY,** once daily (see also Chapter 3).

- Penicillin G Benzathine Injection Suspension (use only for congenital syphilis): 50,000 units/kg, **IM route ONLY,** one-time dose (see also Chapter 3).

Infant Dosing (>1 mo)

- Penicillin G K^+ or Na^+ (aqueous penicillin): 50,000 units/kg/dose IV every 6 hours
- Penicillin G Benzathine or Procaine Injection Suspensions: same as neonatal dosing

Formulations and Administration

- Penicillin G K^+ or Na^+ (aqueous penicillin)
  - IV: reconstitute with sterile water to 500,000 units/mL, then dilute further with D5W to 50,000 units/mL. Infuse over 15–30 minutes.
  - Penicillin G potassium contains 0.084 mEq K+ per each 50,000 units of penicillin. A 15-minute infusion of a 50,000 U/kg dose will deliver potassium at a rate of 0.34 mEq/kg/h.
  - When infusion pump libraries do not accept numbers in the 10,000 and above range, consider having each 1,000 units of penicillin = 1 unit for pump operation.
  - IM: reconstitute and dilute in sterile water to 100,000 units/mL. Although the IV route is preferred for meningitis, adequate serum concentrations are achieved when given IM in neonates and may be considered when treating those with difficult IV access.
  - Unit Conversion: 50,000 units = 30 mg.
- Penicillin G injectable suspensions
  - Penicillin G benzathine is approved for manufacture in 3 sizes of prefilled syringes: 600,000 units per 1 mL, 1,200,000 units per 2 mL, and 2,400,000 units per 4 mL. Penicillin G procaine is the same, except no 4 mL size.
  - Not all sizes are consistently commercially available, and syringe barrels are not marked with graduations.
  - Whichever size syringe is available, assume a 600,000 unit/mL concentration and aseptically transfer the calculated dose to a 1 mL syringe; include 0.05 mL of overfill to account for volume lost in the dead space of the administration needle.
  - Do not dilute.
  - Administer by IM route only. IV or intra-arterial administration can lead to necrosis, compartment syndrome, gangrene, and death.
  - Viscosity of the suspensions requires use of a 21-gauge needle to administer.
  - Penicillin G injectable suspensions are long acting because of their slow release from the site of injection due to the viscous lecithin-carboxymethylcellulose suspension that forms a compact drug depot. Procaine and benzathine also have low aqueous solubility, which slows dissolution in muscle tissue. Benzathine has lower solubility

than procaine and, hence, it has the slowest dissolution in muscle and is the longest acting.

- Note: A combination product for IM administration exists containing both penicillin G benzathine and penicillin G procaine (Bicillin C-R) and is not appropriate for congenital syphilis. Do not use it.

Main Toxicities: usually well tolerated in neonates when used at the appropriate dose and given by the appropriate route. Pain at IV or IM injection site is common in adults but has not been evaluated in neonates. The Jarisch-Herxheimer reaction (fever, rigors, vomiting, tachycardia, hypotension, hyperventilation, flushing, exacerbation of skin lesions) is not known to occur in neonates with congenital syphilis treated with penicillin; however, it is theoretically possible, particularly if the spirochete load is very high. Maternal Jarisch-Herxheimer reactions to penicillin can occur and cause increased uterine contractions and frequency of fetal deceleration.

Piperacillin/Tazobactam

Administered: IV **Excreted: Renally**

Piperacillin is a modified ampicillin molecule. Like ampicillin, it has excellent activity against *Enterococcus* and GBS but with expanded activity against gram-negative pathogens including *Enterobacter, Proteus,* and *Pseudomonas.* Alone, piperacillin is susceptible to hydrolysis by many beta-lactamases. Combining it with the beta-lactamase inhibitor tazobactam (piperacillin/tazobactam) allows it to be active against common beta-lactamase producers such as MSSA, the gut anaerobes *Bacteroides* and *Prevotella,* and some ESBL-producing *Escherchia coli* and *Klebsiella.* However, this also makes it unnecessarily broad spectrum for single-organism coverage if susceptible to narrower-spectrum agents (eg, tobramycin for *Pseudomonas,* nafcillin for MSSA).

Tazobactam is not active against most ampC beta-lactamase. Treatment failure is possible when piperacillin/tazobactam is used alone to treat ampC-producing gram-negative bacilli (cefepime is preferred). Failure is also possible when used to treat some ESBL-producing *E coli* and *Klebsiella* (meropenem is preferred). Piperacillin/tazobactam also has poor CSF penetration and has not been studied for treatment of pediatric meningitis. It, therefore, has limited utility in the NICU other than anaerobic or polymicrobial coverage for focal, non-CNS infections where ESBL or ampC-producing Enterobacteriales are not identified or not likely (eg, surgical NEC with negative blood culture results).

Pharmacodynamics: Time above MIC

Susceptible Isolate MIC: Enterobacteriales ≤8/2 mg/L; *Pseudomonas aeruginosa* and anaerobes ≤16/4 mg/L

Neonatal Dosing (0–60 DOL)[a]

GA <32 wk		GA ≥32 wk	
PNA <14 days	PNA ≥14 days	PNA <14 days	PNA ≥14 days
80 mg/kg q8h	80 mg/kg q8h	80 mg/kg q8h	100 mg/kg q8h

[a] Based on piperacillin component. The recommendations in the dosing table are >90% likely to achieve concentrations >16 mg/L for 75% of the dosing interval.

Infant Dosing (>2 mo): 80 mg/kg q8h for IAI and q6h for nosocomial pneumonia due to *P aeruginosa* if not susceptible to narrower-spectrum agents.

Formulation and Administration

- IV: 20 mg/mL (piperacillin component): reconstitute a 2.25 g piperacillin/tazobactam vial with 10 mL sterile water for injection to create a 180 mg piperacillin/mL solution. Combine 5.6 mL of the 180 mg/mL solution with 44.4 mL D5W to create a final 20 mg/mL dilution. Administer over 30 min. Avoid rapid administration. Extended infusions are unnecessary for neonates and young infants.

Main Toxicities: usually well tolerated in neonates based on small studies. Reversible and likely benign elevations in plasma creatinine due to inhibition of renal organic anion transport is known to occur in critically ill adults and children. Use of anaerobic antibiotics such as piperacillin/tazobactam can alter gut anaerobes and is associated with worse respiratory health outcomes compared to non–anti-anaerobic agents in adults. Use of broad-spectrum agents such as piperacillin/tazobactam enriches drug-resistant genes in the neonatal fecal microbiome, and in very low birth weight neonates it is associated with an increased risk of candidiasis as with other broad-spectrum therapy (see Chapter 7).

Vancomycin

Administered: IV **Excreted: Renally**

Vancomycin is a glycopeptide antibacterial effective against gram-positive bacteria including *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Clostridia* species, *Corynebacterium* species, and *Bacillus* species. In neonates, vancomycin is limited to treatment of methicillin-resistant *Staphylococcus* species and ampicillin-resistant *Enterococcus.* Vancomycin is less active against methicillin-susceptible *Staphylococcus aureus* compared with beta-lactam antistaphylococcal agents such as cefazolin and nafcillin. Vancomycin is not active against gram-negative bacteria.

Pharmacodynamics: Time above MIC, AUC:MIC

Susceptible Isolate MIC: *Staphylococcus* ≤2 mg/L, *Enterococcus* ≤4 mg/L

Dosing (<60 days of age)

- Begin with a 20 mg/kg loading dose.

≤28 wk GA			>28 wk GA		
SCr	**Dose (mg/kg)**	**Frequency**	**SCr**	**Dose (mg/kg)**	**Frequency**
<0.5	15	q12h	<0.7	15	q12h
0.5–0.7	20	q24h	0.7–0.9	20	q24h
0.8–1.0	15	q24h	1.0–1.2	15	q24h
1.1–1.4	10	q24h	1.3–1.6	10	q24h
>1.4	15	q48h	>1.6	15	q48h

- This dosing is highly reliable for achieving trough concentrations of 5–10 mg/L. There is controversy regarding the best concentration target for neonates. A 24-hour AUC:MIC of at least 400 mg·h/L has become popular based on studies of invasive MRSA infections in adults. This target has not been clinically confirmed in neonates.
- For centers where invasive MRSA infection is relatively common, an online dosing tool is available that should improve the likelihood of empirically achieving AUC ≥400: https://neovanco.insight-rx.com/neo-vanco.
- The AUC is best calculated from 2 concentration measurements rather than 1. In situations in which AUC calculation is not feasible, a trough concentration of 10–11 mg/L is very highly likely (>90%) to achieve AUC ≥400 in any neonate. Setting a target trough of 10–15 mg/L is, therefore, reasonable when treating MRSA. However, troughs as low as 7 mg/L can still achieve an AUC ≥400 in some preterm neonates due to their slower clearance. Thus, AUC is preferred over trough monitoring to prevent unnecessary overexposure.
- For isolates with MIC = 2, achieving an AUC:MIC exposure ≥400 will be difficult, and an alternative antibiotic should be considered (eg, ceftaroline).

- Creatinine concentrations normally fluctuate and are partly influenced by transplacental maternal creatinine in the first week after birth. Cautious use of creatinine-based dosing strategy with frequent reassessment of renal function and vancomycin serum concentrations are recommended in neonates 7 days old and in any neonate with unstable creatinine.

Continuous Infusion Dosing Alternative: 10 mg/kg loading dose over 1 hour followed by

GA (wk)	Continuous dose[a,b] (mg/kg/day)
24–<27	25
27–<30	30
30–<32	35
≥32	40
Term	50

[a] If >7 days PNA and SCr <0.8 mg/dL.

[b] Sample random serum concentration 6–12 h after starting infusion. Goal 15–25 mg/L.

Formulations and Administration

Dilute to 5 mg/mL in D5W or physiologic (normal) saline prior to IV administration. Infuse over 1–2 hours.

Main Toxicities: usually well tolerated. Nephrotoxicity (increased serum creatinine) more likely when trough >15 mg/L or AUC >800 with intermittent dosing.

3. Bacterial Infections in Neonates

NOTES

- Strength of recommendations by authors: A = strong, B = good, C = adequate. See also Introduction.
- Level of Evidence (See also Introduction.)
  - I = High-quality neonatal data
  - II = Less than high-quality neonatal data, extrapolation from other populations
  - III = Case reports or expert opinion
- Antibiotic dosages and additional drug information can be found in Chapter 2 if not given within the tables in this chapter.
- Administration of intravenous (IV) ceftriaxone while receiving IV calcium, including calcium in parenteral nutrition, by the same or different infusion tubing should be avoided. Fatal reactions with ceftriaxone-calcium precipitates in lungs and kidneys in neonates have occurred with rapid IV push ceftriaxone administration. The safety of slower ceftriaxone infusions in the setting of concomitant IV calcium is not known.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Conjunctivitis		
Ocular discharge, mild tearing, and eyelid edema or matting may be caused by nasolacrimal duct obstruction or overgrowth of commensal bacteria and not necessarily infectious conjunctivitis or ophthalmia neonatorum. Non-pharmacological intervention, such as duct massage and saline irrigation administered by properly trained caregivers or parents, can be effective as first-line treatment. Persistent symptoms may be due to bacterial overgrowth and may respond to empiric treatment with broad-spectrum ophthalmic antibacterial agents that have good efficacy and safety in neonates, such as polymyxin/trimethoprim drops or polymyxin/bacitracin ointment. In recalcitrant cases or neonates with alarming findings such as conjunctival swelling or edema (chemosis), moderate to severe mucopurulent discharge or tearing, and eyelid edema, infectious conjunctivitis caused by one of the following pathogens is likely and should be managed with a conjunctival swab sent for diagnostic testing (Gram stain and culture, direct antigen testing, PCR) and targeted systemic ± topical antibiotic therapy.		
– Chlamydial	Azithromycin 10 mg/kg/day PO for 1 day, then 5 mg/kg/day PO for 4 days (AII) or erythromycin ethylsuccinate PO for 10–14 days (AII)	Systemic treatment preferred over topical to prevent development of pneumonia; association of erythromycin and pyloric stenosis in young neonates. Alternative: azithromycin 10 mg/kg/dose once daily for 3 days, although safety not well defined in neonates (CIII). IV azithromycin may be used at the same dose if unable to take PO (AIII). Oral sulfonamides may be used after the immediate neonatal period for infants who do not tolerate erythromycin.
– Gonococcal	Cefotaxime 50 mg/kg IV, IM once AND azithromycin 10 mg/kg PO q24h for 5 days (AIII)	Cephalosporin monotherapy not recommended due to increasing resistance. Susceptibility testing not usually available in the clinical setting. Ceftriaxone is an alternative to cefotaxime in neonates not at risk for hyperbilirubinemia or IV calcium drug interactions (see Notes). Neonatal azithromycin data lacking for gonococcal disease; dose given is that recommended for pertussis. IV azithromycin may be used at the same dose if unable to take PO (AIII). Saline irrigation of eyes. Evaluate for chlamydial infection. All neonates born to mothers with untreated gonococcal infection (regardless of symptoms) require therapy.

– *Staphylococcus aureus*	Topical therapy sufficient for mild *S aureus* cases, but oral or IV therapy may be considered for moderate to severe conjunctivitis (AII). MSSA: oxacillin/nafcillin IV or cefazolin (for non-CNS infections) IM, IV for 7 days. MRSA: vancomycin IV.	Aminoglycoside ophthalmic drops or ointment, polymyxin/trimethoprim drops (BIII) Cephalexin PO for mild to moderate disease caused by MSSA No prospective data for MRSA conjunctivitis Increased *S aureus* resistance with ciprofloxacin/levofloxacin ophthalmic formulations Alternatives for MRSA: linezolid, clindamycin IV, PO (BIII)
– *Pseudomonas aeruginosa*	Cefepime/ceftazidime IV or tobramycin/gentamicin IV/IM for 7–10 days (alternatives: meropenem, pip/tazo, amikacin) (BIII)	Include aminoglycoside or polymyxin B–containing ophthalmic drops or ointment as adjunctive therapy.
– Other gram-negative	Aminoglycoside or polymyxin B–containing ophthalmic drops or ointment if mild (AII) Systemic therapy if moderate to severe or unresponsive to topical therapy (AIII)	Duration of therapy is dependent on clinical course and may be as short as 5 days if clinically resolved.
Gastrointestinal infections In addition to antimicrobial therapy, supportive care for gastrointestinal or foodborne infection includes bowel rest, IV fluid or parenteral nutrition, and gastric decompression via intermittent or continuous suctioning through a nasogastric or orogastric tube. Serial radiographs and surgical consultation should be considered if the enteritis is severe or progressing or if there is evidence of bowel rupture.		
– Botulism	BIG-IV (BabyBIG) 50 mg IV once (AI) Trivalent equine botulinal antitoxin not recommended in neonates	BIG-IV provided by the California Department of Health Infant Botulism Treatment and Prevention Program (510/231-7600; www.infantbotulism.org). BIG-IV reduces duration of hospitalization, mechanical ventilation, and intensive care. BIG-IV is most efficacious when given early in the disease course. Therefore, if botulism is suspected, prompt empiric therapy is appropriate. However, efficacy has been demonstrated up to 14 days (AII).

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
– NEC or peritonitis secondary to bowel rupture	Ampicillin IV AND gentamicin AND metronidazole IM, IV for 10–14 days (AII). Clindamycin may be used in place of metronidazole (AII). Alternatives: meropenem (AI); pip/tazo ± gentamicin (AII).	Surgical drainage (AII). Possible benefit of laparotomy over peritoneal drain in one randomized controlled trial. Neonates colonized with *Bacteroides* as early as age 7 days; *Bacteroides* spp are generally susceptible to metronidazole, pip/tazo, and meropenem but are increasingly resistant to clindamycin. Definitive antibiotic therapy based on blood and, if available, peritoneal culture results (aerobic, anaerobic, and fungal); meropenem if ESBL-producing gram-negative bacilli isolated. Antifungal therapy (see Chapter 5) should be added if *Candida* identified in cultures or if neonate is known to be colonized. Fluconazole if susceptible *Candida* species; amphotericin B if unknown or resistant (BIII). If antifungal treatment is not started, fluconazole prophylaxis should be considered for neonates with NEC, as NEC is a major risk factor for subsequent candidiasis (CII). Vancomycin rather than ampicillin if MRSA prevalent. Duration of therapy generally 7–14 days; however, total duration dependent on clinical response and risk of persisting intra-abdominal abscess (AIII). Probiotics may prevent NEC in preterm neonates born ≤1,500 g, but the optimal strain(s), dose, duration, and safety and ideal target subgroups are not fully known.
– *Salmonella* (non-typhi and typhi)	Ampicillin IM, IV (if susceptible) OR cefotaxime/cefepime IM, IV for 7–10 days (AII)	Observe for focal complications (eg, meningitis, arthritis) (AIII). TMP/SMX for focal gastrointestinal infection and low risk for unconjugated hyperbilirubinemia due to interaction between sulfa and bilirubin-albumin binding.

Osteomyelitis, suppurative arthritis

Obtain cultures of bone or joint fluid and blood before antibiotic therapy.

Surgical drainage of pus (AIII).

Duration of therapy dependent on causative organism and normalization of erythrocyte sedimentation rate and C-reactive protein; unless otherwise specified, minimum treatment duration for osteomyelitis is 3 wk and for arthritis is 2–3 wk (AIII).

Converting antibiotic therapy for osteomyelitis from IV to PO for older children and adults who are improving clinically is recommended; however, IV to PO conversion has not been well studied in preterm neonates. Transitioning neonates from IV to PO therapy should be considered carefully on a case-by-case basis (CII).

Physical therapy may be needed (BIII).

– Empiric therapy	Nafcillin/oxacillin IV (or vancomycin if MRSA is a concern) AND cefepime OR gentamicin IV, IM (AIII)	
– Coliform bacteria	Cefepime OR ceftazidime OR ampicillin (if susceptible) (AIII).	Meropenem for ESBL-producing coliforms; cefepime for ampC beta-lactamase–producing coliforms (AIII).
– Gonococcal arthritis and tenosynovitis	Ceftriaxone IV/IM (AIII)	Care must be taken to avoid ceftriaxone and IV calcium drug interactions (see Notes). If chlamydial coinfection has not been excluded, azithromycin 10 mg/kg PO q24h for 5 days (AIII). Neonatal azithromycin data lacking for gonococcal disease; dose given is that recommended for pertussis. IV azithromycin may be used at the same dose if unable to take PO (AIII).
– *S aureus*	MSSA: oxacillin/nafcillin IV (AII) MRSA: vancomycin IV (AIII) OR ceftaroline IV (BII)	Alternative for MSSA: cefazolin (AIII) Alternatives for MRSA: linezolid, clindamycin (if susceptible) (BIII) Addition of rifampin if persistently positive cultures
– Group B streptococcus	Ampicillin or penicillin G IV (AII)	
– *Haemophilus influenzae*	Ampicillin IV OR cefepime IV if ampicillin resistant	Amox/clav PO OR amoxicillin PO if susceptible (AIII)

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Otitis media		
No controlled treatment trials in newborns; if no response, obtain middle ear fluid for culture. In addition to pneumococcus and *Haemophilus,* coliforms and *S aureus* are etiologic pathogens in neonates (AIII).		
– Empiric therapy	Oxacillin/nafcillin AND gentamicin OR cefepime	Alternative: ampicillin/sulbactam (BII). Start with IV therapy and switch to amox/clav PO when clinically stable (AIII).
– *E coli* (therapy of other coliforms based on susceptibility testing)	Cefepime/ceftazidime	Start with IV therapy and switch to PO when clinically stable (AIII). Depending on susceptibility, PO options are amox/clav, or cefpodoxime. For ESBL-producing strains, use meropenem (AII).
– *S aureus*	MSSA: oxacillin/nafcillin IV MRSA: vancomycin or clindamycin IV (if susceptible)	Start with IV therapy and switch to oral therapy when clinically stable. MSSA: cephalexin PO for 10 days (AIII). MRSA: linezolid PO or clindamycin PO (BIII).
– Group A or B streptococci	Penicillin G or ampicillin IV, IM	Start with IV therapy and switch to oral therapy when clinically stable. Amoxicillin 30–40 mg/kg/day PO div q8h for 10 days.
Parotitis, suppurative	Oxacillin/nafcillin IV AND gentamicin IV, IM for 10 days; consider vancomycin if MRSA suspected (AIII).	Usually staphylococcal but occasionally coliform. Antimicrobial regimen without incision/drainage is adequate in >75% of cases.
Pulmonary infections		
– Empiric therapy of the neonate with early onset of pulmonary infiltrates (within the first 72 h after birth)	Ampicillin IV, IM AND gentamicin or ceftazidime/cefepime IV, IM for 10 days; consider treating low-risk neonates for ≤7 days (see Comments).	For newborns with no additional risk factors for bacterial infection (eg, maternal chorioamnionitis) who (1) have sterile blood cultures, (2) have no need for >8 h of oxygen, and (3) are asymptomatic at 48 h into therapy, 4 days may be sufficient therapy, based on limited observational data.
– *Chlamydia trachomatis*	Azithromycin PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII)	Association of erythromycin and azithromycin with pyloric stenosis in neonates and infants treated <6 wk of age

– *Mycoplasma hominis*	Clindamycin PO, IV for 10 days (Organism is resistant to macrolides.)	Pathogenic role in pneumonia not well defined and clinical efficacy unknown; no association with bronchopulmonary dysplasia (BIII)
– Pertussis	Azithromycin 10 mg/kg PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII)	Association of erythromycin and azithromycin with pyloric stenosis in neonates and infants treated <6 wk of age Alternatives: for >1 mo of age, clarithromycin 7.5 mg/kg q12h for 7 days or TMP/SMX 4 mg TMP/kg q12h for 14 days
– *P aeruginosa*	Cefepime IV for 10–14 days (AIII)	Alternatives: ceftazidime AND tobramycin, pip/tazo AND tobramycin, or meropenem
– *S aureus*	MSSA: oxacillin/nafcillin IV (AIII). MRSA: vancomycin IV OR clindamycin IV if susceptible (AIII). Duration of therapy depends on extent of disease (pneumonia vs pulmonary abscesses vs empyema) and should be individualized with therapy up to 21 days or longer.	Alternative for MSSA: cefazolin IV Addition of rifampin or linezolid if persistently positive cultures (AIII) Thoracostomy drainage of empyema
– Group B streptococcus	Penicillin G IV OR ampicillin IV, IM for 10 days (AIII)	For serious infections, ADD gentamicin for synergy until clinically improved. No prospective, randomized data on the efficacy of a 7-day treatment course.
– *Ureaplasma* spp (*urealyticum* or *parvum*)	Azithromycin PO, IV 20 mg/kg once daily for 3 days (BII)	Pathogenic role of *Ureaplasma* not well defined and BPD prophylaxis not currently recommended. Clinical trials have not shown benefit to azithromycin treatment of *Ureaplasma*-colonized preterm neonates. Many *Ureaplasma* spp resistant to erythromycin Association of erythromycin and pyloric stenosis in neonates

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Sepsis and meningitis		
Duration of therapy: 10 days for sepsis without a focus (AIII); minimum of 21 days for gram-negative meningitis (or at least 14 days after CSF is sterile) and 14–21 days for group B streptococcal meningitis and other gram-positive bacteria (AIII). There are no prospective, controlled studies on 5- or 7-day courses for mild or presumed sepsis.		
– Initial therapy, organism unknown	Ampicillin IV AND a second agent, either gentamicin IV/IM (AII) or cefotaxime/cefepime IV (AII)	Cephalosporin preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII). For neonates colonized with ESBL-producing gram-negative bacilli, or for locations with a high rate (≥10%) of ESBL-producing gram-negative bacilli, empiric therapy with meropenem is preferred over cephalosporins. Initial empiric therapy of nosocomial infection should be based on each hospital's pathogens and susceptibilities. **Essential:** Always narrow antibiotic coverage once susceptibility data are available.
– *Bacteroides fragilis*	Metronidazole or meropenem IV, IM (AIII) or pip/tazo IV (BII)	Alternative: clindamycin, but increasing resistance reported
– *Enterococcus* spp	Ampicillin IV, IM AND gentamicin IV, IM (AIII); for ampicillin-resistant organisms: vancomycin AND gentamicin IV (AIII)	Gentamicin needed with ampicillin or vancomycin for bactericidal activity; continue until clinical and microbiological response documented (AIII). For vancomycin-resistant enterococci that are also ampicillin resistant: linezolid (AIII).
– *E coli*	Cefepime/ceftazidime IV or gentamicin IV, IM (AII)	Cephalosporins preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII). For neonates colonized with ESBL-producing *E coli*, or locations with a high rate (≥10%) of ESBL-producing *E coli*, empiric therapy with meropenem is preferred over cephalosporins.

– Gonococcal	Ceftriaxone OR cefepime OR ceftazidime (AIII) IV	Duration of cephalosporin therapy: 7 days for bacteremia/sepsis (AII), 10–14 days if meningitis is suspected or confirmed (BII). If chlamydial coinfection has not been excluded, azithromycin 10 mg/kg PO q24h for 5 days (AIII). Neonatal azithromycin data lacking for gonococcal disease; dose given is that recommended for pertussis. IV azithromycin may be used at the same dose if unable to take PO (AIII). Care must be taken to avoid ceftriaxone and IV calcium drug interactions (see Notes).
– *Listeria monocytogenes*	Ampicillin IV, IM AND gentamicin IV, IM (AIII)	Gentamicin is synergistic in vitro with ampicillin. Continue gentamicin until clinical and microbiological response documented (AIII).
– *Neisseria meningitidis*	Ceftriaxone OR cefepime OR ceftazidime IV (AI)	Duration of therapy: 7 days for bacteremia/sepsis (AII), 10–14 days if meningitis is suspected or confirmed (BII)
– *P aeruginosa*	Cefepime IV OR ceftazidime IV, IM AND tobramycin IV, IM (AIII)	Meropenem or cefepime is a suitable alternative (AIII). Pip/tazo should not be used for CNS infection.
– *S aureus*	MSSA: oxacillin/nafcillin IV, IM or cefazolin IV, IM (AII) MRSA: vancomycin IV (AIII)	Alternatives for MRSA: clindamycin, linezolid, ceftaroline Cefazolin does not adequately enter the CNS to treat meningitis.
– *Staphylococcus epidermidis* (or any coagulase-negative staphylococci)	Vancomycin IV (AIII)	If organism susceptible, cefazolin (if no CNS focus) or oxacillin/nafcillin are alternatives. Add rifampin if cultures persistently positive. Alternatives: linezolid, ceftaroline.
– Group A streptococcus	Penicillin G or ampicillin IV (AII)	
– Group B streptococcus	Ampicillin or penicillin G IV AND gentamicin IV, IM (AI)	Continue gentamicin until clinical and microbiological response documented (AIII). Duration of therapy: 10 days for bacteremia/sepsis (AII); minimum of 14 days for meningitis (AII).

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Skin and soft tissues		
Oxacillin/nafcillin has greater efficacy against MSSA than vancomycin, and MSSA is more common than MRSA in most nurseries. Therefore, oxacillin/nafcillin is preferred over vancomycin for empiric therapy of skin and soft tissue infection unless the neonate is colonized with MRSA or local prevalence of MRSA is high (AII).		
Omphalitis and necrotizing funisitis can be severe infections due to the proximity of these soft tissue structures to the umbilical blood vessels, and IV therapy is indicated. For mild to moderate skin infections, convalescent oral therapy can be considered if infection responds quickly to IV therapy in adherent families with ready access to medical care (CIII).		
– Empiric therapy for omphalitis/funisitis	Gentamicin AND clindamycin IV for ≥10 days (AII)	Severe omphalitis/funisitis should be managed as suspected necrotizing fasciitis, as per above. Need to culture to direct therapy. For suspect MRSA: add vancomycin in place of clindamycin. Alternative for combined MSSA and anaerobic coverage: pip/tazo. Appropriate wound management for infected cord and necrotic tissue (AIII).
–Necrotizing fasciitis	Pip/tazo IV AND vancomycin IV AND clindamycin IV (AII), or meropenem AND vancomycin IV (BI)	Prompt surgical debridement necessary (AII). Consultation with pediatric ID specialist is recommended for necrotizing fasciitis (AII). Clindamycin blocks toxin formation and improves outcomes in necrotizing fasciitis due to group A streptococci (AII). Substitute meropenem for pip/tazo if neonate is colonized with ESBL-producing gram-negative bacilli.
– Omphalitis/funisitis due to group A or B streptococci	Penicillin G IV for ≥7–14 days (shorter course for superficial funisitis without invasive infection) (AII)	Group A streptococcus usually causes "wet cord" without pus and with minimal erythema; single dose of benzathine penicillin IM adequate.
– Omphalitis/funisitis due to *S aureus*	MSSA: oxacillin/nafcillin IV, IM for ≥5–7 days (shorter course for superficial funisitis without invasive infection) (AIII) MRSA: vancomycin (AIII)	Assess for bacteremia and other focus of infection. Alternatives for MRSA: linezolid, clindamycin (if susceptible).

– Omphalitis/funisitis due to *Clostridium* spp	Clindamycin OR penicillin G IV for ≥10 days, with additional agents based on culture results (AII)	Crepitation and rapidly spreading cellulitis around umbilicus Mixed infection with other gram-positive and gram-negative bacteria common
– Breast abscess	Oxacillin/nafcillin IV, IM for MSSA; vancomycin IV for MRSA	Gram stain of expressed pus guides therapy; ADD ceftazidime/cefepime OR gentamicin if gram-negative rods seen on Gram stain (AIII). Choose empiric vancomycin if neonate is MRSA colonized or MRSA is prevalent in community; alternatives to vancomycin: ceftaroline, clindamycin, linezolid; may need surgical drainage to minimize damage to breast tissue. Treatment duration individualized until clinical findings have completely resolved (AIII).
– Impetigo neonatorum	MSSA: oxacillin/nafcillin IV, IM OR cephalexin PO (AIII) MRSA: vancomycin IV for 5 days (AIII)	Systemic antibiotic therapy usually not required for superficial impetigo; local chlorhexidine cleansing may help with or without topical mupirocin (MRSA or MSSA) or bacitracin (MSSA). Alternatives for MRSA: clindamycin IV/PO or linezolid IV/PO.
– *S aureus* cellulitis or skin abscess	MSSA: oxacillin/nafcillin IV, IM (AII) MRSA: vancomycin IV (AIII) or ceftaroline IV (AIII)	Surgical drainage may be required. MRSA may progress to necrotizing fasciitis. Monitor response to therapy closely. Alternatives for MRSA: clindamycin IV or linezolid IV.
– Group A streptococcus (including erysipelas)	Penicillin G IV for 5–7 days, followed by oral therapy (if bacteremia not present) to complete a 10-day course (AIII)	Alternative: ampicillin. Group B streptococcus may produce similar cellulitis or nodular lesions.
– Group B streptococcus cellulitis	Penicillin G IV OR ampicillin IV, IM	Usually no pus formed Treatment course dependent on extent of infection, 7–14 days

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Syphilis, congenital (<1 mo of age) Evaluation and treatment do not depend on mother's HIV status. Obtain follow-up serology every 2–3 mo until nontreponemal test nonreactive or decreased 4-fold. Laboratory evaluation is indicated for all neonates born to mothers with syphilis if ANY of the following conditions are met: 1) The neonate's physical examination shows signs consistent with congenital syphilis (eg, rash, rhinorrhea, hepatosplenomegaly). 2) The neonate's RPR/VDRL is ≥4 times the maternal RPR/VDRL. 3) The mother did not receive treatment, was treated with a non-penicillin regimen, or completed treatment ≤4 wk before delivery. Laboratory evaluation guides type and duration of therapy and includes CSF analysis (VDRL, cell count, protein), CBC, and platelet count. Other tests, as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmologic examination, and newborn hearing screening. Laboratory evaluation is not indicated when the mother was adequately treated >4 weeks before delivery, the neonate's physical examination is normal, and the neonate's RPR/VDRL is not >2 times the maternal RPR/VDRL.		
– Proven or highly probable disease: (1) abnormal physical examination or laboratory evaluation; (2) serum quantitative nontreponemal serologic titer 4-fold higher than mother's titer; or (3) positive dark field or fluorescent antibody test of body fluid(s)	Aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (AII)	Evaluation: CSF analysis, CBC with differential, long-bone radiographs. If CSF positive, repeat spinal tap with CSF VDRL at 6 mo and, if abnormal, re-treat. If >1 day of therapy is missed, entire course is restarted.
– Normal physical examination, serum quantitative nontreponemal serologic titer not 4-fold higher than maternal titer, and maternal treatment was (1) none, inadequate, or undocumented; (2) erythromycin, azithromycin, or other non-penicillin regimen; or (3) <4 wk before delivery.	Evaluation abnormal or not done completely: aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (AII) Evaluation normal: aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin	Evaluation: CSF analysis, CBC with differential, long-bone radiographs. If >1 day of therapy is missed, entire course is restarted. If all components of the evaluation are obtained and are normal, some experts would not treat but would instead give the single dose of benzathine penicillin G. Reliable follow-up important if only a single dose of benzathine penicillin given.

	G 50,000 U/kg IM q24h for 10 days; OR benzathine penicillin G 50,000 units/kg/dose IM in a single dose (AIII)	
– Normal physical examination, serum quantitative nontreponemal serologic titer ≤ maternal titer, mother treated adequately during pregnancy and >4 wk before delivery; no evidence of reinfection or relapse in mother	Benzathine penicillin G 50,000 units/kg/dose IM in a single dose (AIII)	No evaluation required. Some experts would not treat but provide close serologic follow-up.
– Normal physical examination, serum quantitative nontreponemal serologic titer ≤ maternal titer, mother's treatment adequate before pregnancy	No treatment	No evaluation required. Some experts would treat with benzathine penicillin G 50,000 U/kg as a single IM injection, particularly if follow-up is uncertain.
Syphilis, congenital (>1 mo of age)	Aqueous crystalline penicillin G 200,000–300,000 U/kg/day IV div q4–6h for 10 days (AII)	Evaluation to determine type and duration of therapy: CSF analysis (VDRL, cell count, protein), CBC, and platelet count. Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and hearing evaluation. If no clinical manifestations of disease, CSF examination is normal, and CSF VDRL test result is nonreactive, some specialists would treat with up to 3 weekly doses of benzathine penicillin G 50,000 U/kg IM. Some experts would provide a single dose of benzathine penicillin G 50,000 U/kg IM after 10 days of parenteral treatment, but value of this additional therapy is not well documented.
Tetanus neonatorum	Metronidazole IV, PO (alternative: penicillin G IV) for 10–14 days (AIII) Human TIG 500 U IM for 1 dose (AIII)	Wound cleaning and debridement vital; IVIG (200–400 mg/kg for 1 dose) is an alternative if TIG not available; equine tetanus antitoxin not available in the United States but is alternative to TIG.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Tuberculosis		
For children <2 y, tuberculin skin testing is preferred over interferon-gamma release assays for detection of TB infection (AII).		
Evaluation for TB disease in neonates should include chest radiographs, sputum or gastric aspirate sampling for culture, and lumbar puncture. Consultation with pediatric ID specialist is recommended.		
All tuberculosis therapy for neonates is given as oral therapy once daily unless otherwise indicated.		
– Prophylaxis following exposure to close contact with TB disease	If source case has clinical signs and symptoms of TB, an abnormal chest radiograph, and/or positive sputum testing, a full evaluation for TB disease in the neonate should be performed. If TB active disease excluded, neonate should receive isoniazid 10–15 mg/kg/day for 3–4 mo and then retested with a tuberculin skin test. Alternative: rifampin 15–20 mg/kg/day for 9 mo may be used for latent TB infection due to isoniazid-resistant organisms (AII).	If infant's repeat skin testing at 3–4 mo is positive, evaluation for TB disease should be repeated. If negative, isoniazid can be discontinued unless source case remains infectious or has poor adherence to treatment. Isoniazid/rifapentine 12-wk prophylaxis not studied or recommended in neonates. If source case has positive tuberculin skin testing or interferon-gamma release assay but a negative chest radiograph, infection is unlikely, and no workup or treatment is indicated. Pyridoxine (vitamin B_6) supplementation recommended while on isoniazid; concentration in common liquid multivitamins is sufficient. Vitamin B_6 deficiency is rare in pediatric TB treatment.
Suspected or proven TB disease without CNS involvement	Isoniazid 10–15 mg/kg/day AND rifampin 15–20 mg/kg/day PO for at least 6 mo (AI). ADD pyrazinamide 30–40 mg/kg/day AND ethambutol 15–25 mg/kg/day for first 2 mo (AI).	Drug regimen should be based on susceptibility testing. If no positive cultures from neonate, the infectious contact's susceptibility testing should be used. DOT highly preferred (AII). Rifabutin not recommended in neonates.

Suspected or proven TB disease with CNS involvement	Isoniazid 10–15 mg/kg/day AND rifampin 15–20 mg/kg/day for at least 6 mo AND corticosteroids for first 4–6 wk (AI) (AI). ADD pyrazinamide 30–40 mg/kg/day AND amikacin 15–30 mg/kg/day OR ethionamide 15–20 mg/kg/day for first 2 mo (AI).	Drug regimen should be based on susceptibility testing. If no positive cultures from neonate, mother's susceptibility testing should be used. DOT highly preferred (AII).

Urinary tract infection

In infants with grades 1–4 vesicoureteral reflux, antibiotic prophylaxis reduces recurrences but increases likelihood of recurrences being due to resistant organisms and does not affect renal scarring. There are limited data regarding the role of antibiotic prophylaxis for grade 5 vesicoureteral reflux.

In general, long-term antibiotic prophylaxis for vesicoureteral reflux is not recommended. The risks and benefits of short-term prophylaxis should be considered on an individual basis (BII). If antibiotic prophylaxis is used, agent selection should be based on local pathogen prevalence and susceptibilities.

– Initial therapy, organism unknown	Ampicillin AND gentamicin; OR ampicillin AND cefotaxime/cefepime pending culture and susceptibility test results for 7–10 days	Renal ultrasound and voiding cystourethrogram indicated after first UTI to identify abnormalities of urinary tract. Oral therapy acceptable once neonate asymptomatic and culture sterile.
– Coliform bacteria (eg, *E coli, Klebsiella, Enterobacter, Serratia*)	Cefotaxime/cefepime IV, IM OR, in absence of renal or perinephric abscess, gentamicin IV, IM for 7–10 days (AII)	Ampicillin used for susceptible organisms
– *Enterococcus*	Ampicillin IV, IM for 7 days for cystitis, may need 10–14 days for pyelonephritis, add gentamicin until cultures are sterile (AIII); for ampicillin resistance, use vancomycin, add gentamicin until cultures are sterile.	Gentamicin needed with ampicillin or vancomycin for synergistic bactericidal activity (assuming organism susceptible).
– *P aeruginosa*	Ceftazidime IV, IM OR, in absence of renal or perinephric abscess, tobramycin IV, IM for 7–10 days (AIII)	Meropenem or cefepime are alternatives.

4. Viral Infections in Neonates

NOTES

- Strength of recommendations by authors: A = strong, B = good, C = adequate. See also Introduction.
- Level of Evidence (See also Introduction.)
  - I = High-quality neonatal data or US Food and Drug Administration approval
  - II = Less than high-quality neonatal data, extrapolation from other populations
  - III = Case reports or expert opinion
- Antibiotic dosages and additional drug information can be found in Chapter 2 if not given within the tables in this chapter.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Cytomegalovirus		
– Congenital, moderate to severe symptomatic disease OR isolated sensorineural hearing loss	For moderately to severely symptomatic neonates: Oral valganciclovir at 16 mg/kg/dose PO bid for 6 mo (AI). IV ganciclovir 6 mg/kg/dose IV q12h can be used for some of or all the first 6 wk of therapy if oral therapy not advised but provides no added benefit over oral valganciclovir (AII). An "induction period" starting with IV ganciclovir is not recommended if oral valganciclovir can be tolerated. For isolated sensorineural hearing loss: Oral valganciclovir at 16 mg/kg/dose bid for 6 wk	Benefit for hearing loss and neurodevelopmental outcomes (AI). Dosing should be adjusted periodically (eg, monthly) for infant weight gain. Treatment recommended for neonates with moderate or severe symptomatic congenital CMV disease, with or without CNS involvement, and for neonates with isolated sensorineural hearing loss. Note that the durations of therapy differ for these conditions, with 6 mo recommended for the former and 6 wk recommended for the latter (AI). Treatment for congenital CMV should start within the first 12 wk after birth (ie, before postnatal week 13). Neutropenia develops in 20% (oral valganciclovir) to 68% (IV ganciclovir) of neonates on long-term therapy (responds to G-CSF or temporary discontinuation of therapy). Absolute neutrophil counts should be performed weekly for 6 wk, then at 8 wk, then monthly for the duration of antiviral treatment; serum ALT concentration should be measured monthly during treatment. CMV-IVIG not recommended for neonates.
– Congenital, mild symptomatic disease without hearing loss	None	Unless there is evidence of hearing loss, treatment is not routinely recommended for "mildly symptomatic" neonates congenitally infected with CMV (eg, only 1 or perhaps 2 manifestations of congenital CMV infection, which are mild in scope [eg, isolated IUGR, mild hepatomegaly] or transient and mild in nature [eg, a single platelet count of 80,000 or an ALT of 130, with these numbers serving only as examples]), as the risks of treatment may not be balanced by benefits in mild disease.
– Congenital, asymptomatic infection	None	Treatment for asymptomatic neonates congenitally infected with CMV should not be given.
– Perinatally or postnatally acquired	Ganciclovir 12 mg/kg/day IV div q12h for 14–21 days (AIII)	Antiviral treatment has not been studied in this population but can be considered in patients with acute, severe, visceral (end-organ) disease, such as pneumonitis, hepatitis, encephalitis, necrotizing enterocolitis, or

		persistent thrombocytopenia. If such patients are treated with parenteral ganciclovir, a reasonable approach is to treat for 2 wk and then reassess responsiveness to therapy. If clinical and laboratory data suggest benefit of treatment, an additional 1 wk of parenteral ganciclovir can be considered if symptoms and signs have not fully resolved. Oral valganciclovir is not recommended in these more severe disease presentations. Observe for possible relapse after completion of therapy (AIII).
Enterovirus	Supportive therapy, no antivirals currently FDA approved Some experts would administer immune globulin, 750 mg/kg IV as a single dose for neonates with severe disease (CIII)	Pocapavir is currently under investigation for enterovirus (poliovirus) and may be available for compassionate use. Pleconaril PO is currently under consideration for submission to FDA for approval for treatment of neonatal enteroviral sepsis syndrome. As of October 2023, it is not available for compassionate use.
Hepatitis B		
Newborns infected perinatally with HBV are at >90% risk for chronic infection. Prophylaxis with hepatitis B vaccine and immune globulin is highly effective for prevention of infection.		
There is no FDA-approved treatment for infants <1 y, but it may take up to a year before a diagnosis of perinatal transmission of hepatitis B can be made.		
– Prophylaxis following perinatal exposure to HBV (HBsAg-positive mother)	HBV pediatric single antigen vaccine, 0.5 mL IM once AND hepatitis B immune globulin, 0.5 mL IM once (AI)	Prophylaxis is most effective when given within 12 h of birth. HBV pediatric single antigen vaccine should be given within 12 h to all exposed neonates (ie, those whose mothers are HBsAg positive). If maternal hepatitis B status (HBsAg) is unknown and neonate's birth weight is ≥2 kg, HBV pediatric single antigen vaccine should be given within 12 h of birth; hepatitis B immune globulin may be delayed but should be given as soon as the mother's HBsAg returns positive or within 7 days or at hospital discharge (whichever is first) if mother's HBsAg remains unknown. If maternal hepatitis B status is unknown and neonate's birth weight is <2 kg, hepatitis B immune globulin should be given within 12 h of birth along with HBV pediatric single antigen vaccine. Vaccine and immune globulin should be administered in different thighs.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Hepatitis C	None	Perinatal transmission is approximately 5%. Sensitivity and specificity of hepatitis C PCR of blood at age 2–6 mo is high. Treatment for children <3 y is not recommended. There are no FDA-approved treatments for this age group, and chance of spontaneous resolution over the first 3 y following birth is approximately 25%. However, neonates with confirmed hepatitis C infection should be referred to a pediatric ID specialist or pediatric liver diseases specialist for long-term monitoring to determine status at 3 y, at which time antiviral therapy can be administered if the patient is still positive.
Herpes simplex virus infection (HSV-1 and HSV-2) Neonatal HSV infection is classified as skin, eyes, and/or mouth disease; CNS disease; or disseminated disease depending on extent of infection. A full diagnostic evaluation, including surface and vesicle swabs for PCR or viral culture, blood and CSF HSV PCR, and ALT, is necessary to properly classify neonates, as duration of therapy is determined by disease classification. Neonates with CNS disease who have skin involvement are classified as CNS. Neonates with disseminated disease who have CNS or skin involvement are classified as disseminated disease. Neonates who survive HSV disease, regardless of classification, should receive suppressive therapy with PO acyclovir, 300 mg/m^2/dose tid for 6 mo after completion of parenteral therapy (AI). Monitor for neutropenia at 2 and 4 wk after initiating suppressive acyclovir therapy and then monthly during suppressive therapy.		
– Skin, eyes, and/or mouth disease	Acyclovir 60 mg/kg/day div q8h IV for 14 days (AII). Infuse IV doses over 1 h and maintain neonate normovolemia to decrease risk of renal toxicity. If eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel (AII).	An ophthalmologist should be involved in management and treatment of acute neonatal ocular HSV disease. Different IV acyclovir dosages have been modeled, but no clinical data are available in humans to support their use. Unlike CSF HSV PCR, there is no recommendation to recheck a previously positive blood HSV PCR near end of therapy. Foscarnet for acyclovir-resistant disease.

– CNS disease, with or without skin, eyes, and/or mouth disease involvement	Acyclovir 60 mg/kg/day div q8h IV for 21 days (AII). Infuse IV doses over 1 h and maintain neonate normovolemia to decrease risk of renal toxicity. If eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel (AII).	Different IV acyclovir dosages have been modeled, but no clinical data are available in humans to support their use. Perform CSF HSV PCR near end of 21 days of therapy and continue IV acyclovir until CSF PCR negative. Unlike CSF HSV PCR, there is no recommendation to recheck a previously positive blood HSV PCR near end of therapy. Foscarnet for acyclovir-resistant disease. Refer to a pediatric ID specialist for suspected or documented acyclovir resistance.
– Disseminated disease with or without CNS involvement	Acyclovir 60 mg/kg/day div q8h IV for 21 days (AII). Infuse IV doses over 1 h in a well-hydrated neonate to decrease risk of renal toxicity. If eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel (AII).	Different IV acyclovir dosages have been modeled, but no clinical data are available in humans to support their use. Serum AST/ALT may help identify early disseminated infection, although the sensitivity and specificity of elevation of transaminases in neonatal HSV disseminated disease is not known. For babies with CNS involvement, perform CSF HSV PCR near end of 21 days of therapy and continue IV acyclovir until CSF PCR negative. Unlike CSF HSV PCR, there is no recommendation to recheck a previously positive blood HSV PCR near end of therapy. Foscarnet for acyclovir-resistant disease. Refer to a pediatric ID specialist for suspected or documented acyclovir resistance.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Human immunodeficiency virus		
The prophylaxis and evaluation of HIV-exposed newborns varies based on risk. High-risk neonates require additional antiviral agents and longer durations of prophylaxis than low-risk neonates.		
A neonate with a positive HIV test result or clinical signs of illness consistent with HIV should be referred immediately to an HIV specialist for additional testing and treatment.		
Women with HIV infection in the United States should be counseled against breastfeeding. Limited data suggest that the risk of transmission via human milk is very low for mothers whose viral load is undetectable. However, in the United States, where safe water and affordable infant formula are available, breastfeeding is not recommended. In addition, pre-mastication (pre-chewing) of infant food by HIV-infected caregivers has been associated with HIV transmission and should be avoided.		
– Prophylaxis following low-risk perinatal exposure (mother received antiretroviral therapy during pregnancy and had sustained viral suppression near delivery)	ZDV for the first 4 wk of age (AI). May reduce to 2 wk for some low-risk situations (BII). GA ≥35 wk: ZDV 8 mg/kg/day PO div q12h OR 6 mg/kg/day IV div q12h. GA 30–34 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 2 wk of age to 6 mg/kg/day PO (OR 4.5 mg/kg/day IV) div q12h. GA ≤29 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 4 wk of age to 6 mg/kg/day PO (OR 4.5 mg/kg/day IV) div q12h.	For detailed information, go to https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new (updated January 31, 2023; accessed October 20, 2023). UCSF Clinician Consultation Center (888/448-8765) provides free clinical consultation. Start prevention therapy as soon after delivery as possible but by 6–8 h of age for best effectiveness (AII). Monitor CBC at birth and 4 wk (AII). Perform HIV-1 DNA PCR or RNA assays at 14–21 days, 1–2 mo, and 4–6 mo (AI). Perinatal HIV infection can be presumptively excluded once HIV-1 PCRs at 14–21 days and 1–2 mo are negative. Perinatal HIV infection can be definitively excluded once HIV-1 PCR after age 4 mo is also negative. Initiate TMP/SMX prophylaxis for pneumocystis pneumonia at 6 wk of age if HIV infection not yet presumptively excluded (AII). TMP/SMX dosing is 2.5–5 mg/kg/dose of TMP component PO q12h.

– Prophylaxis following high-risk perinatal exposure (mothers with primary HIV infection during pregnancy, OR who were not treated before delivery, OR who were treated but did not achieve undetectable viral load before delivery)	ZDV and 3TC for 6 wk AND either NVP or RAL (BII) ZDV dosing same as described above for low-risk exposure; in infants ≥35 wk of gestation, the dosage should be increased to 12 mg/kg/day PO div q12 once the infant is >4 wk of age. 3TC dosing (≥32 wk of gestation) Birth–4 wk: 4 mg/kg/day PO div q12h >4 wk: 8 mg/kg/day PO div q12h NVP dosing (≥37 wk of gestation at birth) Birth–4 wk: NVP 12 mg/kg/day PO div q12h	Delivery management of women with HIV who are receiving antiretroviral therapy and have viral loads between 50 and 999 copies/mL varies. Data do not show a clear benefit to IV ZDV and cesarean delivery for these women. Decisions about the addition of NVP, 3TC, or RAL for neonates born to these mothers should be made in consultation with a pediatric ID specialist. NVP dosing and safety not established for neonates whose birth weight <1.5 kg. The Panel on Treatment of HIV in Pregnancy and Prevention of Perinatal Transmission recommends using "treatment" antiretroviral regimens for high-risk, exposed neonates to preclude infection or to increase the chance of HIV remission or cure. This was initially inspired by the experience of a baby from Mississippi, a high-risk neonate treated within the first 2 days after birth with subsequent infection documentation; the neonate went off therapy at 18 mo without evidence of circulating virus until 4 y of age, at which point HIV became detectable. Clinical trials are ongoing to study these issues further.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
	>4 wk: NVP 400 mg/m^2/day of BSA PO div q12h; make this dose increase only for infants with confirmed HIV infection. NVP Dosing (≥34–<37 wk of gestation at birth) Birth–1 wk: NVP 8 mg/kg/day PO div q12h 1–4 wk: NVP 12 mg/kg/day PO div q12h >4 wk: NVP 400 mg/m^2/day of BSA PO div q12h; make this dose increase only for infants with confirmed HIV infection. RAL dosing ≥37 wk of gestation at birth and ≥2,000 g Birth–1 wk: qd dosing at about 1.5 mg/kg/dose 2–<3 kg: 0.4 mL (4 mg) qd 3–<4 kg: 0.5 mL (5 mg) qd 4–<5 kg: 0.7 mL (7 mg) qd 1–4 wk: bid dosing at about 3 mg/kg/dose 2–<3 kg: 0.8 mL (8 mg) bid 3–<4 kg: 1 mL (10 mg) bid 4–<5 kg: 1.5 mL (15 mg) bid 4–6 wk: bid dosing at about 6 mg/kg/dose 3–<4 kg: 2.5 mL (25 mg) bid 4–<6 kg: 3 mL (30 mg) bid 6–<8 kg: 4 mL (40 mg) bid	When empiric treatment is used for high-risk neonates and HIV infection is subsequently excluded, NVP, 3TC, and/or RAL can be discontinued and ZDV can be continued for 6 wk total. Consider consultation with a pediatric ID specialist, especially when considering use of RAL (CIII). If the mother has taken RAL within 2–24 h before delivery, the neonate's first dose of RAL should be delayed until 24–48 h after birth; other antiretroviral drugs should be started as soon as possible.

– Treatment of confirmed HIV infection	Combination antiretroviral therapy with ≥3 drugs is recommended for all neonates regardless of clinical status or laboratory values (AI). ZDV (same as prophylaxis dosing) AND 3TC: age <4 wk, 4 mg/kg/day PO div bid; age ≥4 wk, 8 mg/kg/day PO div bid AND either NVP 12 mg/kg/day PO div bid OR RAL: age <1 wk, 1.5 mg/kg PO qd; age 1–4 wk, 6 mg/kg/day PO div bid; age ≥4 wk, 12 mg/kg/day PO div bid	Consultation with a pediatric HIV specialist highly recommended. UCSF Clinician Consultation Center (888/448-8765) provides free clinical consultation. NVP dose should be lowered to 4 mg/kg/dose PO bid for preterm neonates age 0–7 days; after age 7 days, can increase to regular dose. NVP dosing and safety not established for neonates whose birth weight <1.5 kg. RAL dosing and safety not established for preterm neonates. For neonates and infants who are ≥14 days AND ≥42 wk PMA (corrected GA), LPV/r (300 mg/75 mg/m^2/dose PO bid) may be used instead of NVP or RAL. Toxicity concerns preclude its use before age 14 days and 42 weeks PMA. If LPV/r is used, dose must be adjusted frequently for weight gain. TMP/SMX prophylaxis for pneumocystis pneumonia is indicated for all HIV-infected neonates and infants age <1 y regardless of CD4 cell count/percentage (AI). TMP/SMX dosing is 2.5–5 mg/kg/dose of TMP component PO q12h.
– Prophylaxis following *postnatal* exposure (eg, blood, semen from a known HIV-infected individual) AND <72 h since exposure	Age 4 wk–<2 y: 4 wk of prophylaxis with: ZDV 24 mg/kg/day PO div bid AND 3TC 8 mg/kg/day PO div bid (age 1–3 mo); 10 mg/kg/day PO div bid (age >3 mo) PLUS EITHER RAL 25 mg/dose PO bid (3–<4 kg), 30 mg/dose PO bid (4–<6 kg) OR LPV/r 600 mg LPV/m^2/day PO div bid (BIII)	Consultation with a pediatric HIV specialist is advised. No evidence regarding management of postnatal exposure in neonates and infants age <4 wk. Prophylaxis not recommended if >72 h since exposure.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Influenza A and B viruses	Oseltamivir Preterm, <38 wk PMA: 1 mg/kg/dose PO bid Preterm, 38–40 wk PMA: 1.5 mg/kg/dose PO bid Preterm, >40 wk PMA: 3 mg/kg/dose PO bid Term, birth–8 mo: 3 mg/kg/dose PO bid 9–11 mo: 3.5 mg/kg/dose PO bid	Oseltamivir chemoprophylaxis (qd instead of bid dosing) not recommended for neonates and infants <3 mo unless the situation is judged critical (eg, breastfeeding mother with documented influenza) because of limited safety and efficacy data in this age group. Post-exposure oseltamivir chemoprophylaxis has been used in limited circumstances for high-risk neonates and infants (eg, severe chronic lung disease, mechanical ventilation), but there are limited safety and efficacy data in this age group (CIII). Parenteral peramivir is approved in the United States for use in infants and children ≥6 mo; no pharmacokinetic or safety data exist in neonates. Zanamivir (inhaled) and baloxavir not approved or recommended for neonates or infants. Oral baloxavir is approved in the United States for use in persons ≥5 y; no pharmacokinetic or safety data exist in neonates. The adamantanes, amantadine and rimantadine, are not currently effective due to near-universal resistance of influenza A.
Respiratory syncytial virus		
– RSV treatment	Ribavirin (6-g vial to make 20 mg/mL solution in sterile water), aerosolized over 18–20 h daily for 3–5 days (BII)	Aerosolized ribavirin provides little benefit and should only be considered for use in life-threatening RSV infection. Airway reactivity with inhalation precludes routine use. No prospective data on oral ribavirin. Neither palivizumab nor nirsevimab provides benefit in the treatment of active RSV infection.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
– RSV prophylaxis	Nirsevimab is approved and recommended over palivizumab, but for the 2023–2024 RSV season nirsevimab may not be widely available. Nirsevimab, 50 mg/dose (or 100 mg/dose if ≥5 kg) IM once per season. If nirsevimab not available: palivizumab 15 mg/kg IM monthly (max 5 doses)	Nirsevimab for all neonates and infants <8 mo entering first RSV season. Only infants at high risk should receive a second dose of nirsevimab before their second RSV season. For situations where nirsevimab is not available, palivizumab should continue to be used only for high-risk infants: those born before 29 wk 0 days' gestation or any preterm infant with chronic lung disease, and infants of any gestational age with hemodynamically significant heart disease. Clinicians may administer palivizumab prophylaxis to neonates and infants with neuromuscular or pulmonary abnormalities that impair airway clearance or those who are profoundly immunocompromised (CIII). Insufficient data to recommend use of palivizumab for neonates with Down syndrome or cystic fibrosis. Infants who develop RSV infection despite palivizumab should not receive additional monthly prophylaxis. Palivizumab prophylaxis is not recommended for prevention of health care–associated RSV disease.
Varicella-zoster virus		
– VZV treatment	Acyclovir 20 mg/kg/dose IV q8h	Active vesicular disease should be treated promptly. Neonates with congenital varicella syndrome (cicatricial skin scarring, ocular lesions, neurologic lesions, and/or limb lesions) do not require treatment unless there are active vesicles.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
– VZV prophylaxis	Neonates whose mother has varicella 5 days before to 2 days after delivery: varicella zoster immune globulin 125 units/10 kg body weight IM if >2 kg, max 625 units (ie, 5 vials); 62.5 units IM if ≤2 kg Exposure of neonates <28 wk gestation or birth weight ≤1,000 g to person with varicella or zoster, regardless of maternal VZV immunity: varicella zoster immune globulin, 125 units/10 kg body weight IM if >2 kg, max 625 units (ie, 5 vials); 62.5 units IM if ≤2 kg Exposure of neonates ≥28 wk gestation, whose mother lacks evidence of VZV immunity, during the first 2–3 mo after birth to person with varicella or zoster: varicella zoster immune globulin, 125 units/10 kg body weight IM if >2 kg, max 625 units (ie, 5 vials); 62.5 units IM if ≤2 kg	Postexposure prophylaxis with varicella zoster immune globulin is not necessary in neonates ≥28 wk gestation whose mothers have confirmed VZV immunity by history or serologic testing. If varicella zoster immune globulin not available, IVIG 400 mg/kg once OR oral acyclovir (20 mg/kg/dose, 4 times daily) beginning 7–10 days after exposure and continuing for 7 days can be used instead.

5. Fungal Infections in Neonates

NOTES

- Strength of recommendations by authors: A = strong, B = good, C = adequate. See also Introduction.
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  - II = Less than high-quality neonatal data, extrapolation from other populations
  - III = Case reports or expert opinion
- Antibiotic dosages and additional drug information can be found in Chapter 2 if not given within the tables in this chapter.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Aspergillosis (usually cutaneous infection with systemic dissemination)	Voriconazole dosing never studied in neonates but likely initial dosing same or higher as children ≥2 y: 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose. Continued dosing is guided by monitoring of trough serum concentrations (AII). When stable, may switch from voriconazole IV to voriconazole PO 18 mg/kg/day div bid (AII). Unlike in adults, PO bioavailability in children is only approximately 60%. PO bioavailability in neonates has never been studied. Trough monitoring is crucial after switch. Alternatives for primary therapy when voriconazole cannot be administered: L-AmB 5 mg/kg/day (AII). ABLC is another possible alternative. Echinocandin primary monotherapy should not be used for treating invasive aspergillosis (CII). AmB-D should be used only in resource-limited settings in which no alternative agent is available (AII).	Aggressive antifungal therapy, early debridement of skin lesions, as this is common presenting finding in neonatal aspergillosis (AIII). Voriconazole is the preferred primary antifungal therapy for all clinical forms of aspergillosis (AI). Early initiation of therapy in patients with strong suspicion of disease is important while a diagnostic evaluation is conducted. Therapeutic voriconazole trough serum concentrations of 2–5 mg/L are important for success. It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability. Low voriconazole concentrations are a leading cause of clinical failure. Neonatal and infant voriconazole dosing is not well defined, but doses required to achieve therapeutic troughs are generally higher than in children >2 y (AIII). Voriconazole side effects in adults and children include elevated transaminases, encephalopathy, myoclonus, visual disturbances, photosensitivity, QTc prolongation, and renal injury from accumulation of the solvent in the IV product. These toxicities have not been well evaluated in neonates but may be worse in neonates due to their immature clearance mechanisms and vulnerable developing skin and neural networks. Clinicians should, therefore, monitor closely for toxicities and avoid unnecessary prolonged treatment courses. No experience with posaconazole or isavuconazole in neonates. Total treatment course is a minimum of 6–12 wk, largely dependent on evidence of disease improvement. Salvage antifungal therapy options after failed primary therapy include a change of antifungal class (using L-AmB or an echinocandin), switching to posaconazole (pediatric investigational dose 18 mg/kg/day PO div q8h, goal trough concentrations >1 mg/L), or using combination antifungal therapy.

In vitro data suggest some synergy with 2 (but not 3) drug combinations: an azole plus an echinocandin is the most well studied. If combination therapy is employed, this is likely best done initially when voriconazole trough concentrations may not yet be therapeutic.

Routine susceptibility testing is not recommended but is suggested for patients suspected of having an azole-resistant isolate or who are unresponsive to therapy.

Azole-resistant *Aspergillus fumigatus* is increasing. If local epidemiology suggests >10% azole resistance, empiric initial therapy should be voriconazole with echinocandin OR with L-AmB, and subsequent therapy guided based on antifungal susceptibilities.

Micafungin likely has equal efficacy to caspofungin against aspergillosis.

***Candida* spp**

Most invasive *Candida* infections (candidiasis) in neonates are due to *C albicans,* followed by *C parapsilosis* and *C glabrata*. Candidiasis due to other species occurs less frequently.

Neonates with candidiasis should be thoroughly investigated for end-organ dissemination, as focus of infection will affect antifungal agent selection and duration of therapy. Studies include CSF analysis, echocardiogram, complete abdominal ultrasound including bladder, and retinal examination (AIII).

Central venous catheter removal strongly recommended. Infected CNS devices, including ventriculostomy drains and shunts, should be removed if possible.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
– Candidiasis treatment	AmB-D (1 mg/kg/day IV q24h) is recommended therapy (AII). OR Fluconazole (12 mg/kg/day IV q24h, after a loading dose of 25 mg/kg [or 35 mg/kg if on ECMO]) is an alternative if patient has not been on fluconazole prophylaxis (AII). OR L-AmB (5 mg/kg/day IV q24h) is an alternative but carries a theoretical risk of less urinary tract penetration compared with AmB-D (CIII). Alternatives: micafungin 10 mg/kg/day IV q24h OR caspofungin 25 mg/m^2/day IV q24h (BIII). Flucytosine 100 mg/kg/day PO div q6h can be added for neonates with CNS disease who have not responded to initial AmB-D monotherapy (CIII). Duration of therapy for candidemia without obvious metastatic complications is for 2 wk after documented clearance and resolution of symptoms (therefore, generally 3 wk total).	Neonates are at high risk of UTI and CNS infection, problematic for echinocandins with poor penetration at those sites; therefore, AmB-D is preferred, followed by L-AmB and fluconazole; echinocandins are discouraged, despite their fungicidal activity. Treat *Candida* identified in the urine as systemic infection until proven otherwise. Evaluate for other sites of infection: CSF analysis, echocardiogram, complete abdominal ultrasound including bladder; retinal eye examination. Antifungal susceptibility testing is suggested for serious or persistent disease (particularly for those treated with fluconazole). *C krusei* inherently resistant to fluconazole; *C parapsilosis* may be less susceptible to echinocandins; increasing resistance of *C glabrata* to fluconazole and echinocandins. No proven benefit for combination antifungal therapy in candidiasis. Echinocandins should be used with caution and generally limited to salvage therapy or situations in which resistance or toxicity preclude use of AmB or fluconazole (BIII). Echinocandins are not renally eliminated and should not be used to treat isolated neonatal UTI. Benefit of flucytosine for CNS disease that does not improve with AmB-D is mild and toxicity is common; use with caution. Serum flucytosine concentrations should be obtained after 3–5 days to achieve a 2-h post-dose peak $<$100 mcg/mL (ideally 30–80 mcg/mL) to prevent neutropenia.

– Candidiasis prophylaxis	In nurseries with high rates of candidiasis (>10%), IV or oral fluconazole prophylaxis (AI) (3–6 mg/kg twice weekly for 6 wk) in high-risk neonates (birth weight <1,000 g) is recommended. Oral nystatin 100,000 units tid for 6 wk is an alternative to fluconazole in neonates with birth weights <1,500 g in situations in which availability or resistance precludes fluconazole use (CII). Prophylaxis of neonates and children on ECMO: fluconazole 12 mg/kg on day 1, followed by 6 mg/kg/day (BII).	Prophylaxis can also be considered in high-risk neonates >1,000 g with risk factors for candidiasis, including gastrointestinal pathology (eg, necrotizing enterocolitis, gastroschisis) or prolonged treatment with third- or fourth-generation cephalosporins or carbapenems (CIII). If fluconazole prophylaxis is used, a different antifungal (eg, AmB-D) should be used for empiric therapy.
– Oropharyngeal *Candida* (thrush)	Nystatin, 100,000 units/mL, 4–6 mL PO qid until thrush resolved (AI). Systemic therapy with fluconazole (6 mg/kg/day PO q24h) can be used if topical therapy fails.	Gentian violet not recommended as first-line therapy due to mucosal irritation and staining
– Candidal dermatitis (diaper dermatitis)	Nystatin powder, 100,000 U/g, applied liberally to area 2–3 times daily until dermatitis resolved (AI) OR oral fluconazole (6 mg/kg/day PO q24h)	IV therapy with fluconazole can be used if topical and oral therapy fails.
– Congenital cutaneous candidiasis	AmB for 14 days, or 10 days if CSF culture negative (AII). Fluconazole alternative if *C albicans* or known fluconazole-sensitive *Candida* spp.	Treat promptly when rash presents with full IV dose, not prophylactic dosing or topical therapy. Diagnostic workup includes aerobic cultures of skin lesions, blood, and CSF. Pathology examination of placenta and umbilical cord if possible.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
***Malassezia* spp**	AmB-D 1 mg/kg/day IV q24h (AII). Alternative: L-AmB 5 mg/kg/day IV q24h (BII). Voriconazole dosing never studied in neonates but likely initial dosing same or higher as children ≥2 y: 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose. Continued dosing is guided by monitoring of trough serum concentrations (AII).	Activity of antifungal agents is species dependent. Vascular catheters should be removed promptly, and lipid-containing infusions should be stopped. Therapeutic voriconazole trough serum concentrations of 2–5 mg/L are important for success. It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability. Low voriconazole concentrations are a leading cause of clinical failure. No experience with posaconazole or isavuconazole in neonates. Echinocandins have no antifungal activity against *Malassezia* spp.
Mucormycosis (*Mucor, Rhizopus,* and *Rhizomucor* spp)	AmB-D 1 mg/kg/day IV q24h (AII). If possible, surgical debridement of infected tissue is critical (AII).	Cutaneous and gastrointestinal mucormycosis are the most common manifestations in preterm neonates, with high mortality. Pulmonary and cerebral infections can occur. Consult a pediatric infectious diseases specialist. No recommendation on posaconazole or isavuconazole for neonatal mucormycosis due to limited data. Echinocandins do not have activity against *Mucorales* organisms.
Pneumocystis jiroveci (formerly *carinii*) **pneumonia**	TMP/SMX 15–20 mg TMP component/kg/day IV div q8h (AI) for 3 wk OR, for TMP/SMX-intolerant patients or treatment failure, pentamidine isethionate 4 mg base/kg/day IV daily (BII) for 3 wk	Neonates with severe disease should receive concomitant steroid therapy (AII). Neonates with mild to moderate disease can be transitioned to PO TMP/SMX therapy 15–20 mg TMP component/kg/day PO div qid to complete 3 wk (BII).

6. Parasitic Infections in Neonates

NOTES

- Strength of recommendations by authors: A = strong, B = good, C = adequate. See also Introduction.
- Level of Evidence (See also Introduction.)
  - I = High-quality neonatal data or US Food and Drug Administration approval
  - II = Less than high-quality neonatal data, extrapolation from other populations
  - III = Case reports or expert opinion
- Antibiotic dosages and additional drug information can be found in Chapter 2 if not given within the tables in this chapter.

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Amebiasis (*Entamoeba histolytica*)	Metronidazole 35–50 mg/kg/day PO div q8h, THEN paromomycin 30 mg/kg/day PO div q8h for 10 days	Neonates may present with dysentery, colitis, or hepatic abscess. Extraintestinal disease is rare. For severe disease metronidazole may be given intravenously. Use antibacterial dosing given in Chapter 2. Surgical drainage of liver abscesses generally not required unless medical therapy fails. Limited data on tinidazole use in neonates. Iodoquinol is an alternative luminal agent but may cause gastrointestinal irritation.
Babesiosis (*Babesia microti*)	Atovaquone 40 mg/kg/day PO div q12h AND azithromycin 10 mg/kg/day on day 1 followed by 5 mg/kg/day on subsequent days PO q24h for 7–10 days for mild disease; 10 mg/kg/day, IV, q24h, until symptoms abate, then convert to PO, for at least 7–10 days OR quinine sulfate 24 mg/kg/day PO div q8h for at least 7–10 days AND clindamycin 21–30 mg/kg/day IV div q8h PO (mild disease) or div q6–8h IV (severe disease) for at least 7–10 days	Atovaquone dosing differs from that used for *Pneumocystis* prophylaxis or treatment. Double-volume exchange transfusion should be considered for critically ill neonates (eg, hypotension, severe hemolysis, end-organ failure, >10% parasitemia). Treatment should be extended until parasitemia resolved on peripheral blood smears. Quinine oral syrup is not available in the United States but can be extemporaneously prepared by a pediatric pharmacist from adult-sized oral capsules.
Chagas disease (*Trypanosoma cruzi*)	Benznidazole 5–7.5 mg/kg/day PO div bid for 60 days (AII) Alternative: nifurtimox <40 kg: 10–20 mg/kg/day PO div tid or qid for 60 days (BII)	Nifurtimox is considered second-line therapy due to greater side effects and more limited use data compared with benznidazole. Health care professionals caring for neonates with suspected or proven Chagas disease can contact the CDC Parasitic Diseases Hotline at 404/718-4745 or parasites@cdc.gov. Benznidazole approved for children 2–12 y. Nifurtimox is approved from birth to 17 y in those ≥2.5 kg.

Cryptosporidium	Nitazoxanide 100 mg PO bid for 3 days	No data about use of nitazoxanide in children <1 y; FDA approval for this indication at >1 y. Recovery depends largely on the immune status of the host; treatment is not required in all immunocompetent individuals.
Giardiasis (*Giardia intestinalis*)	Metronidazole 15 mg/kg/day PO div tid (AII)	For reinfection, treatment with the same agent should be used. For resistant infections, an alternative agent should be considered (BIII). Limited data on nitazoxanide and tinidazole use for neonates. Furazolidone (in infants >1 mo) may be considered for refractory disease (not available currently in the United States).

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Malaria		
Up-to-date treatment information is available from the CDC at www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Clinicians are encouraged to consult the treatment tables found on that website for the most detailed and updated information about drugs and dosages when treating malaria.		
CDC Malaria Hotline 770/488-7788 or 855/856-4713 toll-free (Monday–Friday, 9:00 am–5:00 pm ET) or emergency consultation after hours 770/488-7100.		
If malaria develops despite chemoprophylaxis, the agent(s) used for chemoprophylaxis should not be used in the treatment regimen.		
In general, treatment of malaria in neonates should be provided in consultation with a pediatric ID specialist. For chloroquine-sensitive *Plasmodium falciparum, P vivax, and P ovale* (except when acquired in Papua New Guinea or Indonesia); *P malariae;* and *P knowlesi*, chloroquine is the treatment of choice. For resistant strains of *P falciparum* or for severe malaria, combination therapy is indicated as per the following.		
P falciparum from Central America west of the Panama Canal, the Dominican Republic, Haiti, and the majority of the Middle East generally can be considered chloroquine sensitive.		
Severe malaria (any species or region)	Artesunate 2.4 mg/kg/dose IV at 0, 12, and 24 h (BI). If artesunate is unavailable, give oral regimen (per uncomplicated malaria; see next entry) until artesunate arrives. See CDC website for details (www.cdc.gov/malaria/resources/pdf/malaria_treatment_table_202302c.pdf).	Once neonate has stabilized, can take PO, and parasite density is $<$1% at least 4 h after third dose of artesunate, give a complete follow-on regimen as per uncomplicated malaria (see next entry). Evidence supporting exchange transfusion is limited, and exchange transfusion is not recommended by the CDC. Artesunate is available commercially, but if not in stock or not available within 24 h, contact CDC Malaria Hotline (770/488-7788 or 855/856-4713 toll-free, Monday–Friday, 9:00 am–5:00 pm ET; emergency number for after hours, weekends, and holidays: 770/488-7100). For artesunate, WHO guidelines recommend 3 mg/kg/dose IV; CDC guidelines recommend 2.4 mg/kg/dose.

Uncomplicated malaria – *P falciparum,* chloroquine sensitive, OR *P vivax* or *ovale*, chloroquine sensitive, OR *P malariae* OR *P knowlesi*	Chloroquine phosphate OR hydroxychloroquine 10 mg base/kg PO once, followed by 5 mg base/kg PO at 6, 24, and 48 h (AI). May also use any of the options for chloroquine-resistant malaria (see next entry).	Assume chloroquine resistance in *P vivax* malaria acquired in Papua New Guinea and Indonesia. Follow treatment course for *P vivax* or *P ovale* with primaquine 0.5 mg base/kg/day PO q24h for 14 days (AII). Primaquine treatment is effective against the hypnozoite forms of *P vivax* and *P ovale*. Without primaquine therapy, the hypnozoites can remain latent in hepatocytes and reactivate in the future. Neonates *must* be tested for G6PD deficiency before treatment with primaquine, which can cause hemolysis in those with G6PD deficiency. Primaquine is not needed in congenital malaria, as there is no exoerythrocytic stage of the parasite.
– *P falciparum,* chloroquine resistant OR species not identified OR chloroquine-resistant *P vivax* or *P ovale*	Artemether-lumefantrine (Coartem) (1 tab: 20 mg artemether and 120 mg lumefantrine) (BII) 5–<15 kg: 1 tab at 0, 8, 24, 36, 48, and 60 h OR Atovaquone-proguanil (Malarone) (pediatric tab: 62.5 mg atovaquone and 25 mg proguanil) (BII) 5–<8 kg: 2 pediatric tabs PO q24h for 3 days OR Quinine sulfate 30 mg (8.3 mg base)/kg/day PO div tid for 3 days AND clindamycin 20 mg/kg/day PO, IV div tid for 7 days (AII) OR Mefloquine 15 mg/kg PO once, followed by 10 mg salt/kg 6–12 h later (BII)	Dosing is not established for either atovaquone-proguanil OR artemether-lumefantrine for neonates <5 kg. Quinine oral syrup is not available in the United States but can be extemporaneously prepared by a pediatric pharmacist from adult-sized oral capsules. Mefloquine 250 mg tab can be cut in ⅓ or ¼ to provide the closest approximate dose and then crushed and suspended in human milk, formula, or water. If *Plasmodium* spp is subsequently identified as *P vivax* or *P ovale,* follow treatment course with primaquine 0.5 mg base/kg/day PO q24h for 14 days (AII).

RECOMMENDED THERAPY FOR SELECTED CONDITIONS

Condition	Therapy (evidence grade)	Comments
Scabies (*Sarcoptes scabiei*)	Permethrin 5% cream applied to entire body (including scalp), left on for 8–14 h then washed off, repeat in 1 wk (BII); OR crotamiton 10% lotion applied to entire body (including scalp), left on overnight then washed off in am, on days 1, 2, 3, and 8 (BII)	Launder bedding and clothing. Crotamiton treatment failure has been observed. Ivermectin 200 mcg/kg PO once weekly for 2 doses is an alternative if topical therapy fails, but safety not well established in neonates; for individual neonates/infants, the benefits of treatment may outweigh risks. Itching may continue for weeks after successful treatment.
Toxoplasmosis, congenital (*Toxoplasma gondii*)	Sulfadiazine 100 mg/kg/day PO div q12h AND pyrimethamine 2 mg/kg PO daily for 2 days (loading dose), then 1 mg/kg PO q24h for 2–6 mo, then 3 times weekly (Monday, Wednesday, Friday) up to 1 y (AII) Folinic acid (leucovorin) 10 mg 3 times weekly (AII)	Round sulfadiazine dose to 125 or 250 mg, which is ¼ or ½ of a 500-mg tab. OK to crush tab fraction to give with feeding. Round pyrimethamine dose to 6.25 or 12.5 mg, which is ¼ or ½ of a 25-mg tab. OK to crush tab fraction to give with feeding. Prednisone or prednisolone 1 mg/kg/day div q12h if active chorioretinitis or CSF protein $>$1 g/dL (AIII). Start sulfadiazine after neonatal jaundice has resolved. Therapy is only effective against active trophozoites, not cysts.

7. Antimicrobial Stewardship in the Nursery

Antibiotics are among the most-used medications in the nursery setting. Antibiotic use has been associated with unintended adverse outcomes, both at the nursery level (increased prevalence of multidrug-resistant organisms [MDROs] and *Candida;* increased cost) and for individual neonates (increased risk of subsequent sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and death in preterm neonates; increased risk of asthma, eczema, and obesity in term neonates). However, *appropriate antibiotic therapy,* defined as the right dose of the right drug for the right duration, has dramatically improved outcomes for sick newborns. Therefore, our goal is not to eliminate antibiotic use in the nursery but, rather, to minimize inappropriate use. This approach will preserve the benefits of antibiotics while minimizing unintended toxicity, resistance, and cost.

Effective antimicrobial stewardship in the nursery is based on the following 7 principles:

1. Prevent infections. Infections that do not occur at all cannot contribute to antibiotic overuse. Therefore, nursery health care professionals should be diligent in their infection prevention practices. Meticulous hand hygiene is the single most important element of infection prevention and the one that is most germane to well-baby nurseries or couplet care. For sicker neonates who require care in the neonatal intensive care unit (NICU), a bundled approach to indwelling medical devices (eg, central venous catheters, endotracheal tubes), standardized feeding protocols that emphasize human milk, and close attention to hand hygiene for all staff and visitors are critical elements. Screening for MDROs (eg, nasal swabs to detect methicillin-resistant *Staphylococcus aureus* [MRSA] colonization) can inform infection prevention efforts as well as antimicrobial stewardship. For example, a neonate with a negative MRSA screening result can receive oxacillin in lieu of vancomycin if sepsis is suspected. The specific approach to screening, including number of MDROs screened for and frequency of screening, is best tailored to the individual nursery's epidemiology.

2. Optimize diagnostics. Bacterial cultures remain the gold standard for diagnosing neonatal sepsis; newborns cannot be accurately diagnosed with sepsis based on clinical signs alone. Therefore, health care professionals must obtain adequate material for culture before starting antibiotic therapy. A minimum of 1 mL of blood should be cultured; obtaining 2 blood cultures from different sites may help with interpretation of contaminants but is secondary to ensuring adequate culture volume. The sensitivity of 1 mL of blood for culture exceeds 99% for clinically meaningful levels of bacteremia. Urine and cerebrospinal fluid cultures are not routinely indicated for suspected early-onset sepsis ($<$72 h) but should be obtained if late-onset sepsis is suspected ($\geq$72 h). Material from other sterile sites (eg, peritoneal fluid, bone or joint fluid) can be obtained if the clinical situation dictates. Culture from non-sterile sites, such as skin or the trachea, may be helpful in certain circumstances, but care providers must remember that these sites are not sterile and bacteria cultured from these sites may represent colonization

rather than infection. Therefore, culture results from non-sterile sites should only be obtained when pretest probability for infection at that site is high and should be interpreted cautiously.

Some health care professionals also order non-culture laboratory tests of inflammation, including complete blood cell counts with differential, C-reactive protein, procalcitonin, and others. These tests generally have good negative predictive value and can help to exclude infection when cultures are sterile at 36 to 48 hours. However, these tests have poor specificity and positive predictive value because many noninfectious conditions can make them abnormal (eg, perinatal asphyxia, hypothermia, preeclampsia, preterm birth). Therefore, it is critical that health care professionals do not extend the duration of antibiotic therapy based only on abnormal laboratory values when cultures are sterile. Similarly, molecular diagnostic tests, including nucleic-acid–based tests and whole genome sequencing tests, are increasingly used along with cultures. Health care professionals must remember that the negative predictive value of such tests is good but the positive predictive value is unclear because molecular tests can detect killed bacteria (eg, bacteria successfully eradicated by maternal intrapartum antibiotic prophylaxis) as well as extremely low-colony–count sepsis (ie, ≤4 colony-forming units/mL), neither of which require prolonged antimicrobial therapy.

3. Start narrow but effective empiric therapy. The selection of empiric antibiotic therapy for neonates with suspected sepsis should be based on the narrowest spectrum agents that have efficacy against the most likely organisms and penetrate the infected compartments. For early-onset sepsis, ampicillin and gentamicin remain the workhorses for most centers. Group B streptococci are universally susceptible to ampicillin, and most gram-negative enteric pathogens (eg, *Escherichia coli*) remain susceptible to gentamicin. When treating suspected late-onset sepsis, broader gram-positive coverage is needed to cover *S aureus* and coagulase-negative staphylococci; nafcillin, oxacillin, and vancomycin are reasonable choices depending on the local prevalence of MRSA. Routine use of third- and fourth-generation cephalosporins, such as cefotaxime or cefepime, should be avoided if possible due to their association with increased risk for antibiotic resistance and candidiasis. Situations in which third- and fourth-generation cephalosporins are warranted include suspected or proven gram-negative meningitis, acute renal injury for which aminoglycosides are contraindicated, and exposure to maternal gonorrhea.

The treatment for necrotizing enterocolitis varies widely between centers due to lack of consensus about the optimal approach. Regimens that include anaerobic agents have been associated with increased survival. The data are most robust for ampicillin, gentamicin, and metronidazole. Clindamycin has been studied as a replacement for metronidazole, but *Bacteroides* species are increasingly resistant to clindamycin, and clindamycin has been associated with increased risk of stricture formation. Other options include the use of piperacillin/tazobactam monotherapy, piperacillin/tazobactam with an aminoglycoside, or meropenem. Empiric antifungal therapy should also be considered if the neonate is known to be colonized with *Candida*.

Lastly, it is important to note that the selection of empiric antibiotics must be driven by local epidemiology, including NICU- or hospital-wide antibiograms, recent trends (eg, outbreaks), and the neonate's colonization status. In certain situations, these factors may make relatively broad empiric therapy appropriate. The neonate's colonization status should be considered; vancomycin or meropenem are reasonable empiric choices for newborns known to be colonized with MRSA or extended-spectrum beta-lactamase–producing gram-negative bacilli, respectively. If the NICU is currently experiencing an outbreak of a given pathogen, that pathogen should be considered even if the neonate does not have prior colonization (eg, using empiric linezolid for neonates during a vancomycin-resistant *Enterococcus* outbreak). Finally, newborns who are critically ill (eg, hypotensive, severely acidotic, respiratory failure) should receive broad-spectrum empiric coverage while cultures are in process.

4. Narrow therapy. Empiric therapy must be reevaluated as new data become available. In most cases, antibiotics can be discontinued once cultures have been sterile for a sufficient period. For early-onset sepsis, most cultures are positive by 24 to 36 hours; for late-onset sepsis or focal infections, where inoculum may be lower, 48 hours may be needed. If an organism is identified, treatment should be modified to the narrowest-spectrum single effective agent. The use of multiple antibiotics for "synergy" is rarely necessary; conditions that benefit from synergy are highlighted in chapters 3 and 5. Failure to discontinue or narrow therapy once culture results are available is a major driver of antibiotic overuse in the nursery setting.

5. Treat only infections. Antibiotics have no efficacy against noninfectious conditions, viruses, or colonization. Unfortunately, antibiotics often are given for all 3 indications. Treatment of colonizing bacteria cultured from a non-sterile site is unnecessary (eg, vancomycin therapy for light growth of *S aureus* from an endotracheal tube aspirate when the neonate has not had clinical or radiographic signs of pneumonia). In addition, studies have demonstrated that as many as 10% of newborns with signs of late-onset sepsis have respiratory viruses rather than bacterial infection. Finally, prolonged antibiotic therapy for "culture-negative" sepsis is a significant driver of antibiotic use. "Culture-negative" sepsis rates vary widely between and within NICUs and do not correlate with the number of objective risk factors for sepsis. Health care professionals should recognize that clinical signs alone do not reliably differentiate noninfectious conditions from sepsis and should consider alternative diagnoses when cultures are sterile. Discontinuing antibiotics at 36 to 48 hours has not been associated with adverse clinical outcomes.

6. Optimize dosing. Appropriate dosing of antimicrobials in neonates is a challenge. Neonates and young infants have rapidly changing physiology, including absorption, volume of distribution, metabolism, and clearance. These changes are affected by gestational age, chronologic age, and weight. In addition, there are many antimicrobial agents for which neonatal pharmacokinetic data are scant or absent. Unsurprisingly, the complex pharmacokinetics of neonatal antimicrobial therapy mean that careful attention to dosing and, when indicated, therapeutic drug monitoring is necessary to ensure that

pharmacodynamic targets are being achieved while minimizing toxicity. See Chapter 2 for more details.

7. Be accountable. Antimicrobial stewardship in the nursery setting must be a collaboration between nursery care professionals (eg, pediatricians, pharmacists, nurses) and external supporters (eg, infection preventionists, microbiologists, bioinformaticists, infectious diseases specialists). Audit and feedback (ie, collecting information about antibiotic prescribing and presenting it to health care professionals) is a mainstay of stewardship that can inform targeted interventions. Ideally, one or more stakeholders or "champions" should be appointed by the nursery so neonates are appropriately represented within the larger antibiotic stewardship system. Nursery care professionals are more likely to support recommendations and interventions that they have had a share in developing. Finally, stewardship programs should provide ongoing education for health care professionals and trainees.

For neonates with infection, antibiotic therapy is potentially lifesaving. However, inappropriate antibiotic use is harmful rather than helpful. Appropriate antibiotic use in the nursery setting should be based on appropriate diagnostics and dosing strategies. Effective empiric therapy should be discontinued when infection is excluded or optimized when infection is confirmed. Antibiotic stewardship programs, ideally ones that include a nursery champion, are critical to prevent unnecessary use; minimize drug resistance, toxicity, and adverse outcomes; and ensure that effective antimicrobial therapy will continue to be available for neonates who need it.

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